Access DB# 63581

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: DAVID LUKTON Examiner #: 71263 Date: 4/1/02
Art Unit: 1653 Phone Number 30 8-3213 Serial Number: 09/814558
Mail Box and Bldg/Room Location: _____ Results Format Preferred (circle): PAPER DISK E-MAIL
MAIL Box: 9B01 ; Ext. Rm: 9B05
If more than one search is submitted, please prioritize searches in order of need.

****

Title of Invention: Dmt-Tic di- and tri-peptide derivatives and related compositions and methods of use

Applicant: Lazarus

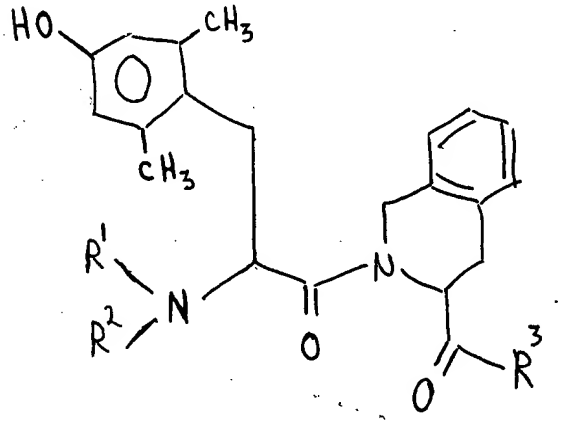
Earliest Priority Date: 3/24/00

* * * * *

Applicants are claiming the compounds below.

R^1 and R^2 are alkyl, or R^1 and R^2 taken together with the nitrogen atom to which they are bonded, represent a 5-membered or 6-membered heterocyclic ring;

R^3 can be anything, but does not contain more than one amino acid.



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STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: _____	NA Sequence (#)_____	STN _____
Searcher Phone #: Alt Contact: Sheppard	AA Sequence (#)_____	Dialog _____
Searcher Location: Tel: 308-4499	Structure (#) _____	Questel/Orbit _____
Date Searcher Picked Up: _____	Bibliographic _____	Dr.Link _____
Date Completed: 4/2/02	Litigation _____	Lexis/Nexis _____
Searcher Prep & Review Time: _____	Fulltext _____	Sequence Systems _____
Clerical Prep Time: _____	Patent Family _____	WWW/Internet _____
Online Time: _____	Other _____	Other (specify)_____

PTO-1590 (8-01)

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FILE COVERS 1907 - 2 Apr 2002 VOL 136 ISS 14
FILE LAST UPDATED: 31 Mar 2002 (20020331/ED)

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CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

The P indicator for Preparations was not generated for all of the CAS Registry Numbers that were added to the CAS files between 12/27/01 and 1/23/02. As of 1/23/02, the situation has been resolved. Searches and/or SDIs in the H/Z/CA/CAplus files incorporating CAS Registry Numbers with the P indicator executed between 12/27/01 and 1/23/02 may be incomplete. See the NEWS message on this topic for more information.

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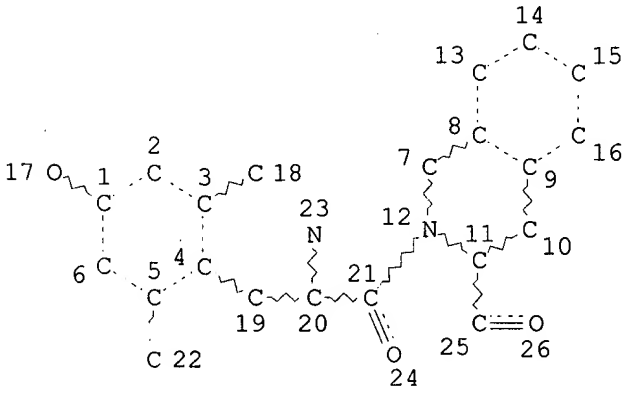

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DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 26

STEREO ATTRIBUTES: NONE
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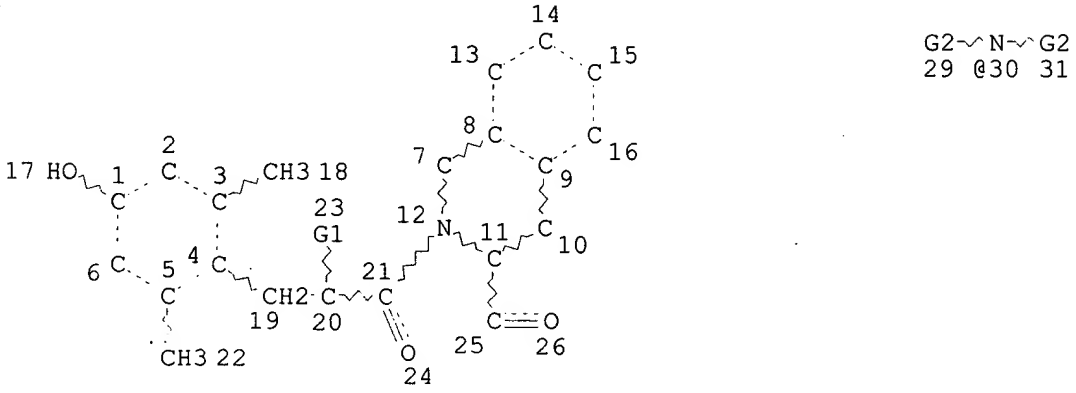
L5 STR



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VAR G2=ME/ET/I-PR/N-PR/I-BU/N-BU/T-BU/S-BU
REP G5=(0-1) A
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 35

STEREO ATTRIBUTES: NONE
L6 28 SEA FILE=REGISTRY SUB=L3 SSS FUL L5
L7 11 SEA FILE=HCAPLUS ABB=ON PLU=ON L6

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=> d ibib abs hitrn l7 1-11

L7 ANSWER 1 OF 11 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:616568 HCAPLUS
DOCUMENT NUMBER: 135:352508
TITLE: Immunosuppression by .delta.-opioid antagonist

naltrindole: .delta.- and triple .mu./.delta./.kappa.-opioid receptor knockout mice reveal a nonopioid activity

AUTHOR(S): Gaveriaux-Ruff, Claire; Filliol, Dominique; Simonin, Frederic; Matthes, Hans W. D.; Kieffer, Brigitte L.

CORPORATE SOURCE: CNRS UPR 9050, ESBS, Universite Louis Pasteur, Illkirch, Fr.

SOURCE: Journal of Pharmacology and Experimental Therapeutics (2001), 298(3), 1193-1198
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The .delta.-opioid antagonist naltrindole has been shown to inhibit graft rejection in vivo and suppress allogeneic mixed lymphocyte reaction (MLR) in vitro, similarly to cyclosporin A. We investigated whether this action is mediated by .delta.-opioid receptors using both genetic and pharmacol. tools. Naltrindole and two related compds., 7-benzylidene-7-dehydronaltrexone and naltriben, inhibited MLR performed with lymphocytes from wild-type and .delta.-opioid receptor knockout mice, with comparable potency. Furthermore, these compds. suppressed the proliferation of spleen cells from triple .delta./.mu./.kappa.-opioid receptor-deficient animals as well. Finally, the highly .delta.-selective, but structurally distinct, antagonist N,N-dimethyl-Dmt-Tic-OH and the general opioid antagonist naltrexone were inactive in the MLR assay. In conclusion, we demonstrate for the first time that the immunosuppressive activity of naltrindole and close derivs. is not mediated by any of the three cloned opioid receptors. Therefore, the postulated inhibitory activity of naltrindole in the graft rejection process is mediated by a target, which remains to be discovered.

IT **178951-49-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(immunosuppression by naltrindole with .delta.- and triple .mu./.delta./.kappa.-opioid receptor knockout mice reveal a nonopioid activity)

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:373100 HCAPLUS

DOCUMENT NUMBER: 135:235885

TITLE: Inhibition of human multidrug resistance P-glycoprotein 1 by analogues of a potent .delta.-opioid antagonist

AUTHOR(S): Lovekamp, T.; Cooper, P. S.; Hardison, J.; Bryant, S. D.; Guerrini, R.; Balboni, G.; Salvadori, S.; Lazarus, L. H.

CORPORATE SOURCE: Peptide Neurochemistry Group, National Institute of Evironmental Health Sciences, LCBRA, Research Triangle Park, NC, 27709, USA

SOURCE: Brain Research (2001), 902(1), 131-134
CODEN: BRREAP; ISSN: 0006-8993

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Analogs of Dmt-Tic (2',6'-dimethyl-l-tyrosine-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid) pharmacophore, a potent

.delta.-opioid receptor antagonist, inhibited hMDR1 P-GP expressed in a G-185 fibroblast cell line in a manner similar to verapamil. N,N(Me)2-Dmt-Tic-NH-1-adamantane, H-Dmt-Tic-NH-1-adamantane, H-Dmt-Tic-Ala-NH-1-adamantane and N,N(Me)2-Dmt-Tic-NH-tBut were highly effective inhibitors. Weaker inhibition was obsd. with N,N(Et)2-Dmt-Tic-OH, H-Dmt-Tic-Ala-NH-tert-Bu amide and cyclo(Dmt-Tic). Results demonstrate that N- and C-terminal hydrophobic/lipophilic analogs of the Dmt-Tic pharmacophore inhibit hMDR1 and point to a potential role as chemosensitizing agents in chemotherapy for cancers contg. hMDR1.

IT **178951-49-0 254101-68-3 254101-89-8**
254101-91-2 359864-93-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of human MDR1 by .delta.-opioid antagonist analogs)

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:828316 HCAPLUS
DOCUMENT NUMBER: 134:66089
TITLE: Opioid pseudopeptides containing heteroaromatic or heteroaliphatic nuclei
AUTHOR(S): Balboni, G.; Salvadori, S.; Guerrini, R.; Bianchi, C.; Santagada, V.; Calliendo, G.; Bryant, S. D.; Lazarus, L. H.
CORPORATE SOURCE: Department of Toxicology, University of Cagliari, Cagliari, I-09126, Italy
SOURCE: Peptides (New York) (2000), 21(11), 1663-1671
CODEN: PPTDD5; ISSN: 0196-9781
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In lieu of H-Dmt-Tic-OH, H-Dmt-analogs included 2-amino-3(1H-benzoimidazol-2-yl)-propionic acid, N(Bzl)Gly, L-octahydroindole-2-carboxylic acid, [3S-(3.alpha.,4a.beta.,8a.beta.)]-decahydro-3-isoquinoline carboxylic acid, benzimidazole-, pyridoindole- or spiroinden-derivs., or C-terminally modified. L- Or D-Ala, Sar, or Pro were spacers between arom. nuclei. Only H-Dmt-(Xaa-)-pyridoindole exhibited high affinities with .delta. and .mu. antagonism. The peptides competed equally against [3H]DPDPE (.delta. agonist) or [3H]N,N(CH3)2-Dmt-Tic-OH (.delta. antagonist) signaling a single .delta. binding site. The data confirm the importance of Tic for .delta. affinity and antagonism, while heterocyclic or heteroaliph. nuclei, or spacer exert effects on .mu.- and .delta.-receptor properties.

IT **178951-49-0**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(opioid pseudopeptides contg. heteroarom. or heteroaliph. nuclei)

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:677175 HCAPLUS
DOCUMENT NUMBER: 134:51294
TITLE: Inverse agonism by Dmt-Tic analogues and HS 378, a naltrindole analogue
AUTHOR(S): Labarre, M.; Butterworth, J.; St-Onge, S.; Payza, K.; Schmidhammer, H.; Salvadori, S.; Balboni, G.;

Guerrini, R.; Bryant, S. D.; Lazarus, L. H.
CORPORATE SOURCE: Department of Pharmacology, AstraZeneca R&D Montreal, St-Laurent, QC, H4S 1Z9, Can.
SOURCE: European Journal of Pharmacology (2000), 406(1), R1-R3
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The potent .delta.-opioid receptor antagonist H-2',6-l-tyrosine(Dmt)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic-OH) exhibited partial inverse agonism (EC50=6.35 nM, Emax=-18.87%) for [35S]GTP.gamma.S binding and H-Dmt-Tic-NH2 was a neutral antagonist (no effect up to 30 .mu.M). In contrast N,N(CH3)2-Dmt-Tic-NH2 was a full inverse agonist (EC50=2.66 nM, Emax=-35.95%) similar to ICI 174864 ([N,N-diallyl-Tyr1,Aib2,3,Leu5]enkephaline) but with a 3.5-fold higher EC50. In comparison, naltrindole was a neutral antagonist while its analog HS 378 was a partial inverse agonist (Emax=-12.99%).
IT **178951-50-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inverse agonism by Dmt-Tic analogs and HS 378)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:288655 HCAPLUS
DOCUMENT NUMBER: 133:99680
TITLE: Tritium labelling of neuropeptides
AUTHOR(S): Toth, Geza; Farkas, Judit; Kertesz, Istvan; Tomboly, Csaba; Darula, Zsuzsanna; Peter, Antal
CORPORATE SOURCE: Institute of Biochemistry, Biological Research Centre, Hungarian Academy of Sciences, Szeged, H-6701, Hung.
SOURCE: Peptides 1998, Proceedings of the European Peptide Symposium, 25th, Budapest, Aug. 30-Sept. 4, 1998 (1999), Meeting Date 1998, 636-637. Editor(s): Bajusz, Sandor; Hudecz, Ferenc. Akademiai Kiado: Budapest, Hung.
CODEN: 68WKAY
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A report from a symposium presenting examples on the tritiation of labeled neuropeptides from synthetic precursor peptides. Catalytic dehalogenation with tritium gas produces radioactive peptides with high specific radioactivity, and with this method, the following new opioid peptides were radiolabeled: endomorphin II (.mu. agonist), N,N-(CH3)2-Dmt-Tic (.delta. antagonist), D-Ala2-D-Nle5-Met-enkephalin-Arg-Phe (.kappa.2 agonist), V-V-hemorphin 7 (Val-Val-Tyr-Pro-Trp-Thr-Gln-Arg-Phe) and dermorphin (.mu. agonist). Precursor peptides were synthesized by solid phase peptide synthesis using the Boc method and the crude peptides were purified on RP-HPLC. The tritiation reaction was carried out on Pd/BaSO4 catalyst with triethylamine to bind the proceeded acid in DMF as solvent with carrier free tritium gas. The crude radiolabeled peptides were purified by RP-HPLC using a radiodetector. Specific radioactivity of the tritiated peptides was then calcd. from the radioactivity and the amt. of the peptide. Finally, the tritiated peptides were stored as ethanolic solns. in liq. nitrogen and the stability of the ligands during storage and under binding conditions was investigated using rat brain membrane and HPLC.
IT **220045-96-5P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological

process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(opioid neuropeptide labeling with tritium and catalytic halogenation using synthetic precursor ligands)

IT **220045-93-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(opioid neuropeptide labeling with tritium and catalytic halogenation using synthetic precursor ligands)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:715597 HCAPLUS
DOCUMENT NUMBER: 132:73213
TITLE: Further Studies on the Dmt-Tic Pharmacophore: Hydrophobic Substituents at the C-Terminus Endow .delta. Antagonists To Manifest .mu. Agonism or .mu. Antagonism
AUTHOR(S): Salvadori, Severo; Guerrini, Remo; Balboni, Gianfranco; Bianchi, Clementina; Bryant, Sharon D.; Cooper, Peter S.; Lazarus, Lawrence H.
CORPORATE SOURCE: Department of Pharmaceutical Science and Biotechnology Center, University of Ferrara, Ferrara, I-441000, Italy
SOURCE: Journal of Medicinal Chemistry (1999), 42(24), 5010-5019
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
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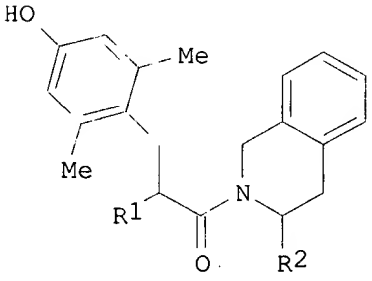

I

AB Twenty N- and/or C-modified Dmt-Tic analogs (I; R1=NH2,CH2NH2,heterocyclics; R2=CH2COOH, COOH, etc.) yielded similar Ki values with either [3H]DPDPE (.delta.1 agonist) or [3H]N,N(Me)2-Dmt-Tic-OH (.delta. antagonist). N-Methylation enhanced .delta. antagonism while N-piperidine-1-yl, N-pyrrolidine-1-yl, and N-pyrrole-1-yl were detrimental. Dmt-Tic-X (X = -NHNH2, -NHCH3, -NH-1-adamantyl, -NH-tBu, -NH-5-tetrazolyl) had high .delta. affinities (Ki = 0.16 to 1 nM) with variable .mu. affinities to yield nonselective or weakly .mu.-selective analogs. N,N-(Me)2Dmt-Tic-NH-1-adamantane exhibited dual .delta. and .mu. receptor affinities (Ki.delta. = 0.16 nM and Ki.mu. = 1.12 nM) and potent .delta. antagonism (pA2 = 9.06) with .mu. agonism (IC50 = 16 nM). H-Dmt-.beta.HTic-OH (methylene bridge between C.alpha. of Tic and carboxylate function) yielded a biostable peptide with high .delta.

affinity (Ki = 0.85 nM) and .delta. antagonism (pA2 = 8.85) without .mu. bioactivity. Dmt-Tic-Ala-X (X = -NHCH3, -OCH3, -NH-1-adamantyl, -NHtBu) exhibited high .delta. affinities (Ki = 0.06 to 0.2 nM) and elevated .mu. affinities (Ki = 2.5 to 11 nM), but only H-Dmt-Tic-Ala-NH-1-adamantane and H-Dmt-Tic-Ala-NHtBu yielded .delta. receptor antagonism (pA2 = 9.29 and 9.16, resp.). Thus, Dmt-Tic with hydrophobic C-terminal substituents enhanced .mu. affinity to provide .delta. antagonists with dual receptor affinities and bifunctional activity.

IT **178951-49-0P 254101-69-4P 254101-71-8P**
254101-73-0P 254101-88-7P 254101-90-1P
254101-92-3P 254101-94-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(studies on opioid pharmacophore, hydrophobic substituents at C-terminus endow .delta. antagonists to manifest .mu. agonism or .mu. antagonism)

REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:410445 HCAPLUS
DOCUMENT NUMBER: 131:214535
TITLE: Tritiation of delta opioid-receptor selective antagonist dipeptide ligands with extraordinary affinity containing 2',6'-dimethyltyrosine
AUTHOR(S): Kertesz, I.; Toth, G.; Balboni, G.; Guerrini, R.; Salvadori, S.
CORPORATE SOURCE: Institute of Biochemistry, Biological Research Centre of the Hungarian Academy of Sciences, Szeged, H-6701, Hung.
SOURCE: Czech. J. Phys. (1999), 49(Suppl. 1, Pt. 2, 13th Radiochemical Conference, 1998), 887-892
CODEN: CZYPAO; ISSN: 0011-4626
PUBLISHER: Institute of Physics, Academy of Sciences of the Czech Republic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recently a new class of .delta. opioid antagonists has been discovered by using Tyr1-Tic2 sequence. The substitution of Tyr1 by Dmt (Dmt = 2',6'-dimethyltyrosine) resulted in a new analog H-Dmt-Tic-OH with enhanced affinity and selectivity. Peptides contg. Tic at position 2 undergo spontaneous diketopiperazine formation in some solvents, and thus, loosing some of their binding ability. To avoid this unwanted side reaction, the authors synthesized the N,N-di-Me analog [N,N(Me)2Dmt-Tic-OH], and it was more stable under storage conditions, but its .delta. affinity declined moderately. On this basis, the authors prepd. the diiodinated analogs of these dipeptides. Catalytic dehalotritiation of precursors resulted in tritiated peptides. High specific radioactivity, 44.67 Ci/mmol with H-[3H2]Dmt-Tic-OH and 59.88 Ci/mmol with N,N(Me)2[3H2]Dmt-Tic-OH were achieved.

IT **220045-96-5P**
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of tritiated 2',6'-dimethyltyrosyl dipeptides as antagonists of .delta.-opioid receptor)

IT **178951-49-0**
RL: RCT (Reactant)
(prepn. of tritiated 2',6'-dimethyltyrosyl dipeptides as antagonists of .delta.-opioid receptor)

IT **220045-93-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of tritiated 2',6'-dimethyltyrosyl dipeptides as antagonists of .delta.-opioid receptor)
IT **220045-94-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of tritiated 2',6'-dimethyltyrosyl dipeptides as antagonists of .delta.-opioid receptor)
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:396671 HCAPLUS
DOCUMENT NUMBER: 131:200061
TITLE: Generation of new Dmt-Tic .delta. opioid antagonists: N-alkylation
AUTHOR(S): Lazarus, Lawrence H.; Salvadori, Severo; Balboni, Gianfranco; Guerrini, Remo; Bianchi, Clementina; Cooper, Peter S.; Bryant, Sharon D.
CORPORATE SOURCE: NIEHS, Research Triangle Park, NC, 27707, USA
SOURCE: Pept. Proc. Am. Pept. Symp., 15th (1999), Meeting Date 1997, 603-604. Editor(s): Tam, James P.; Kaumaya, Pravin T. P. Kluwer: Dordrecht, Neth.
CODEN: 67UCAR
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A symposium with seven refs. A discussion of the opioid antagonist properties of N-alkylated analogs of Tyr-Tic peptide was given.
IT **178951-49-0 178951-50-3 194857-70-0 194857-73-3**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(biol. activity of as .delta. opioid antagonists prepd. via N-alkylation of Dmt-Tic peptide analogs)
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:1815 HCAPLUS
DOCUMENT NUMBER: 130:139633
TITLE: Synthesis of 2',6'-dimethyltyrosine containing tritiated delta opioid-receptor selective antagonist dipeptide ligands with extraordinary affinity
AUTHOR(S): Kertesz, I.; Balboni, G.; Salvadori, S.; Lazarus, L. H.; Toth, G.
CORPORATE SOURCE: Institute of Biochemistry, Biological Research Centre of the Hungarian Academy of Sciences, Szeged, H-6701, Hung.
SOURCE: J. Labelled Compd. Radiopharm. (1998), 41(12), 1083-1091
CODEN: JLCRD4; ISSN: 0362-4803
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A new class of .delta.-opioid antagonists was recently discovered in which the sequence Tyr-Tic was used as a message domain. The substitution of Tyr1 by Dmt (Dmt = 2',6'-dimethyltyrosine) enhanced the .delta. selectivity and antagonist activity. The excellent activity of these ligands was the reason for synthesizing the corresponding tritiated

derivs. Peptides contg. Tic (Tic = 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid) at position 2 undergo spontaneous diketopiperazine formation in some solvents, with a redn. in opioid activity. To avoid this side-reaction, the N,N-di-Me analog [N,N(Me)2-Dmt-Tic-OH] was synthesized and it was found to be stable. Thus, diiodinated forms of H-Dmt-Tic-OH and N,N(Me)2-Dmt-Tic-OH were prepd. to undergo the catalytic dehalotritiation step. Tritiated dipeptides of high specific radioactivity were obtained: 44.67 Ci/mmol for [3H]Dmt-Tic-OH and 59.88 Ci/mmol for [3H]N,N(Me)2-Dmt-Tic-OH.

IT **220045-96-5P**
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(synthesis of dipeptides contg. tritiated dimethyltyrosines as .delta.-opioid receptor antagonists)

IT **178951-49-0**
RL: RCT (Reactant)
(synthesis of dipeptides contg. tritiated dimethyltyrosines as .delta.-opioid receptor antagonists)

IT **220045-93-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(synthesis of dipeptides contg. tritiated dimethyltyrosines as .delta.-opioid receptor antagonists)

IT **220045-94-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of dipeptides contg. tritiated dimethyltyrosines as .delta.-opioid receptor antagonists)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:565015 HCAPLUS
DOCUMENT NUMBER: 127:214595
TITLE: Evolution of the Dmt-Tic Pharmacophore: N-Terminal Methylated Derivatives with Extraordinary .delta. Opioid Antagonist Activity
AUTHOR(S): Salvadori, Severo; Balboni, Gianfranco; Guerrini, Remo; Tomatis, Roberto; Bianchi, Clementina; Bryant, Sharon D.; Cooper, Peter S.; Lazarus, Lawrence H.
CORPORATE SOURCE: Department of Pharmaceutical Science and Biotechnology Center, University of Ferrara, Ferrara, 44100, Italy
SOURCE: J. Med. Chem. (1997), 40(19), 3100-3108
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The .delta. opioid antagonist H-Dmt-Tic-OH (2',6'-dimethyl-L-tyrosyl-1,2,3,4-tetrahydro-3-isoquinoline-3-carboxylic acid) exhibits extraordinary .delta. receptor binding characteristics [Ki.delta. = 0.022 nM; Ki.mu./Ki.delta. = 150 000] and .delta. antagonism (pA2 = 8.2; Ke = 5.7 nM). A change in chirality of Dmt at C.alpha. curtailed .delta. receptor parameters, while replacement of its .alpha.-amino function by a Me group led to inactivity; Tyr-Tic analogs weakly interacted with .delta. receptors. N-Alkylation of H-Dmt-Tic-OH and H-Dmt-Tic-Ala-OH with Me groups produced potent .delta. opioid ligands with high .delta. receptor binding capabilities and enhanced .delta. antagonism: (i) N-Me-Dmt-Tic-OH had high .delta. opioid binding (Ki.delta. = 0.2 nM), elevated .delta. antagonism on mouse vas deferens (MVD) (pA2 = 8.5; Ke = 2.8 nM), and nondetectable .mu. activity with guinea pig ileum (GPI). (Ii) N,N-Me2-Dmt-Tic-OH was equally efficacious in .delta. receptor binding (Ki.delta. = 0.12 nM; Ki.mu./Ki.delta. = 20 000), but .delta. antagonism

rose considerably (pA2 = 9.4; Ke = 0.28 nM) with weak .mu. antagonism (pA2 = 5.8; Ke = 1.58 .mu.M; GPI/MVD = 1:5640). N-Me- and N,N-Me2-Dmt-Tic-Ala-OH also augmented .delta. opioid receptor binding, such that N,N-Me2-Dmt-Tic-Ala-OH demonstrated high affinity (Ki.delta. = 0.0755 nM) and selectivity (Ki.mu./Ki.delta. = 20 132) with exceptional antagonist activity on MVD (pA2 = 9.6; Ke = 0.22 nM) and weak antagonism on GPI (pA2 = 5.8; Ke = 1.58 .mu.M; GPI/MVD = 1:7180). Although the amidated dimethylated dipeptide analog had high Ki.delta. (0.31 nM) and excellent antagonist activity (pA2 = 9.9; Ke = 0.12 nM), the increased activity toward .mu. receptors in the absence of a free acid function at the C-terminus revealed a modest .delta. selectivity (Ki.mu./Ki.delta. = 1 655) and somewhat comparable bioactivity (GPI/MVD = 4500). Thus, the data demonstrate that N,N-(Me)2-Dmt-Tic-OH and N,N-Me2-Dmt-Tic-Ala-OH retained high .delta. receptor affinities and .delta. selectivities and acquired enhanced potency in pharmacol. bioassays on MVD greater than that of other peptide or non-peptide .delta. antagonists.

IT **194857-69-7P 194857-71-1P 194857-72-2P**
194857-74-4P 194857-76-6P
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(prepn. of dimethyltyrosyl isoquinolinecarboxylate derivs. as .delta. opioid antagonists)

L7 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:447008 HCAPLUS
DOCUMENT NUMBER: 125:105145
TITLE: Ultraselective .delta.-opioid mimetic peptides containing dimethyltyrosine and tetrahydroisoquinoline carboxylate and pharmacological and therapeutic uses thereof
INVENTOR(S): Lazarus, Lawrence H.; Salvadori, Severo; Temussi, Piero Andrea
PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9616982	A2	19960606	WO 1995-US15510	19951130
WO 9616982	A3	19961024		
W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5780589	A	19980714	US 1994-347531	19941130
AU 9644639	A1	19960619	AU 1996-44639	19951130
PRIORITY APPLN. INFO.:			US 1994-347531	19941130
			WO 1995-US15510	19951130

OTHER SOURCE(S): MARPAT 125:105145
AB Novel opioid mimetic dipeptides, tripeptides and cyclic peptides exhibit enhanced affinity and selectivity for .delta.-opioid receptors. The

peptides are represented by the formulas L/D-Dmt-L-/D-Tic-R', L/D-R"-Dmt-L/D-Tic-R'; L/D-Dmt-L-/D-Tic-R-R'; L/D-R"-Dmt-L/D-Tic-R-R'; and cyclic (L/D-Dmt-L/D-Tic) wherein Dmt is 2',6'-dimethyl-L/D-tyrosine, Tic is L/D-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, R is a natural or unusual aliph. amino residue, R' is a functional group at the carboxyl terminus of the peptide and R" is a functional group at the amino terminus of the peptide. Pharmacol. and therapeutic compns. are also provided.

IT **178951-49-0 178951-50-3**
RL: BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(.delta.-opioid mimetic; ultraselective .delta.-opioid mimetic peptides contg. dimethyltyrosine and tetrahydroisoquinoline carboxylate and pharmacol. and therapeutic uses thereof)

=> fil caold
FILE 'CAOLD' ENTERED AT 19:11:26 ON 02 APR 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REGlstRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

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L8 0 L6

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=> fil reg
FILE 'REGISTRY' ENTERED AT 19:11:35 ON 02 APR 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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STRUCTURE FILE UPDATES: 31 MAR 2002 HIGHEST RN 403694-27-9
DICTIONARY FILE UPDATES: 31 MAR 2002 HIGHEST RN 403694-27-9

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

The P indicator for Preparations was not generated for all of the CAS Registry Numbers that were added to the H/Z/CA/CAplus files between 12/27/01 and 1/23/02. Use of the P indicator in online and SDI searches during this period, either directly appended to a CAS Registry Number or by qualifying an L-number with /P, may have yielded incomplete results. As of 1/23/02, the situation has been resolved. Also, note that searches conducted using the PREP role indicator were not affected.

Customers running searches and/or SDIs in the H/Z/CA/CAplus files incorporating CAS Registry Numbers with the P indicator between 12/27/01 and 1/23/02, are encouraged to re-run these strategies. Contact the CAS Help Desk at 1-800-848-6533 in North America or 1-614-447-3698, worldwide, or send an e-mail to help@cas.org for further assistance or to receive a credit for any duplicate searches.

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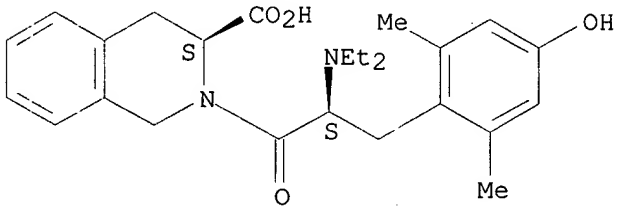
=> d ide can 16 tot

L6 ANSWER 1 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 359864-93-0 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2S)-2-(diethylamino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C25 H32 N2 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:235885

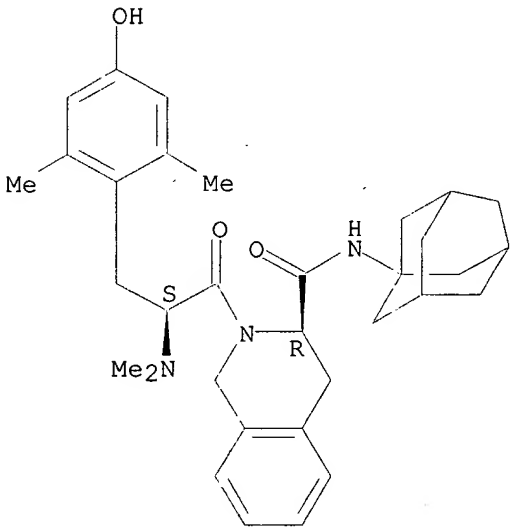
L6 ANSWER 2 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 254101-94-5 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-(dimethylamino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-tricyclo[3.3.1.13,7]dec-

1-yl-, (3R)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C33 H43 N3 O3 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS

CM 1

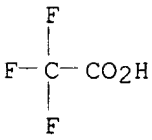
CRN 254101-93-4
CMF C33 H43 N3 O3

Absolute stereochemistry. Rotation (+).



CM 2

CRN 76-05-1
CMF C2 H F3 O2



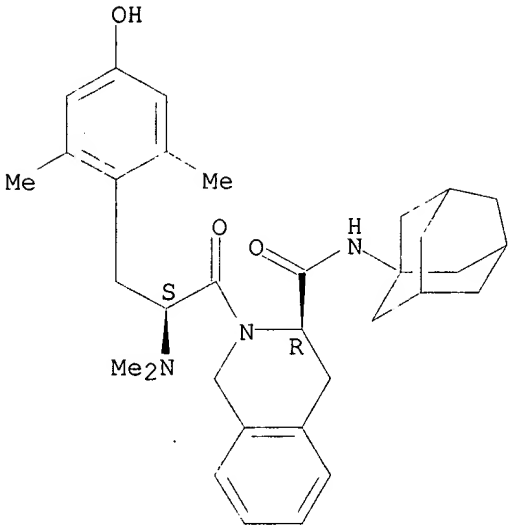
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:73213

L6 ANSWER 3 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 254101-93-4 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-(dimethylamino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-tricyclo[3.3.1.13,7]dec-1-yl-, (3R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH

MF C33 H43 N3 O3
CI COM
SR CA

Absolute stereochemistry. Rotation (+).



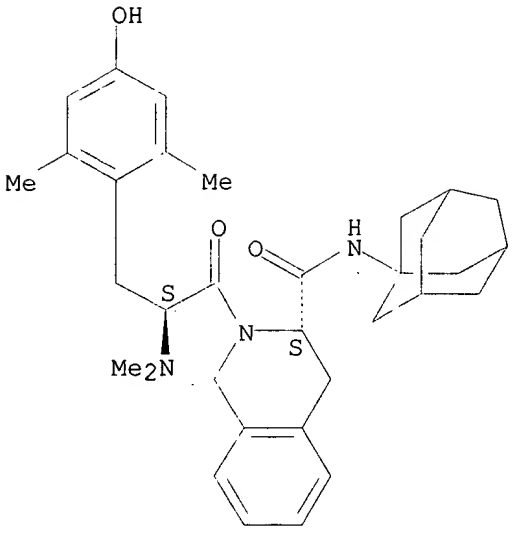
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 ANSWER 4 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 254101-92-3 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-(dimethylamino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-tricyclo[3.3.1.13,7]dec-1-yl-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C33 H43 N3 O3 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS

CM 1

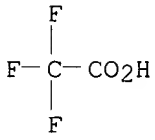
CRN 254101-91-2
CMF C33 H43 N3 O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 76-05-1
CMF C2 H F3 O2

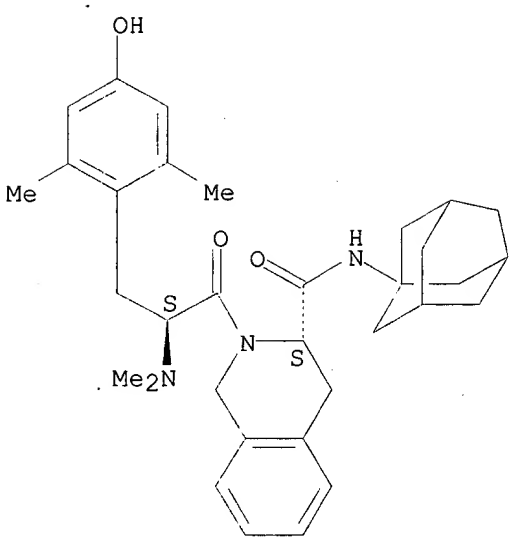


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:73213

L6 ANSWER 5 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 254101-91-2 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-(dimethylamino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-tricyclo[3.3.1.13,7]dec-1-yl-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C33 H43 N3 O3
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:235885

L6 ANSWER 6 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 254101-90-1 REGISTRY
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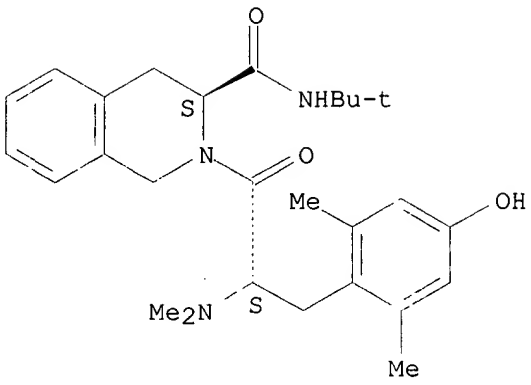
FS STEREOSEARCH
MF C27 H37 N3 O3 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS

CM 1

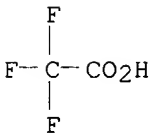
CRN 254101-89-8
CMF C27 H37 N3 O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 76-05-1
CMF C2 H F3 O2

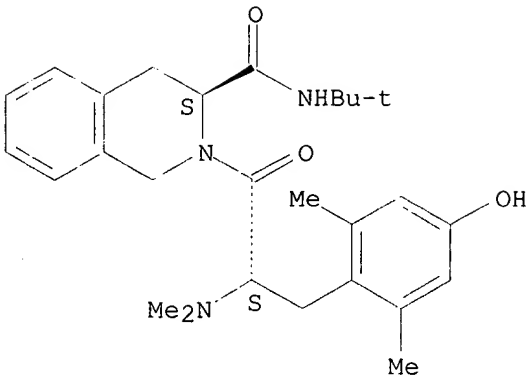


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:73213

L6 ANSWER 7 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 254101-89-8 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-(dimethylamino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-N-(1,1-dimethylethyl)-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H37 N3 O3
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

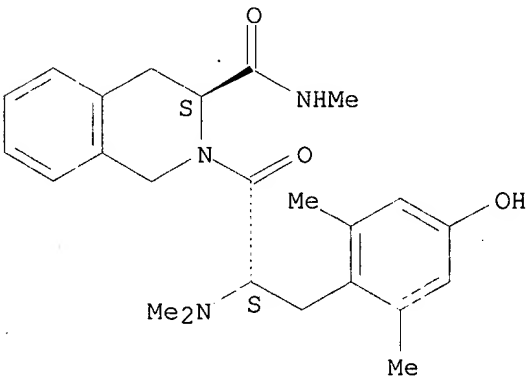
REFERENCE 1: 135:235885

L6 ANSWER 8 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 254101-88-7 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-(dimethylamino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-methyl-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H31 N3 O3 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS

CM 1

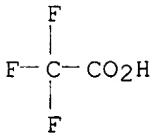
CRN 254101-87-6
CMF C24 H31 N3 O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:73213

L6 ANSWER 9 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 254101-87-6 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-(dimethylamino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-methyl-, (3S)- (9CI) (CA INDEX NAME)
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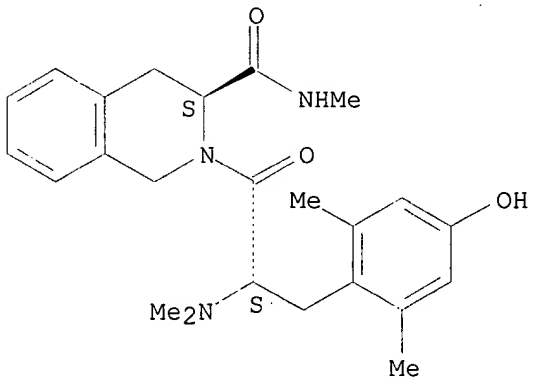
CI COM
SR CA

Absolute stereochemistry. Rotation (-).



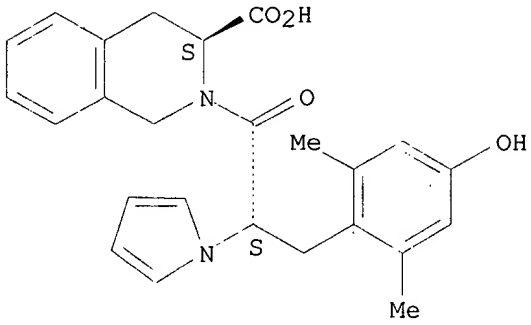
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 ANSWER 10 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 254101-73-0 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 1,2,3,4-tetrahydro-2-[(2S)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxo-2-(1H-pyrrol-1-yl)propyl]-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C25 H26 N2 O4 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS

CM 1

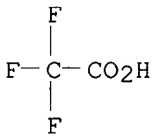
CRN 254101-72-9
CMF C25 H26 N2 O4

Absolute stereochemistry. Rotation (-).



CM 2

CRN 76-05-1
CMF C2 H F3 O2

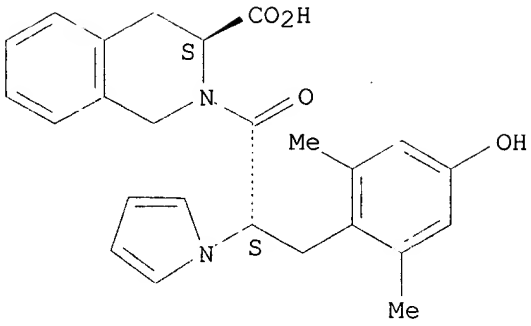


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:73213

L6 ANSWER 11 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 254101-72-9 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 1,2,3,4-tetrahydro-2-[(2S)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxo-2-(1H-pyrrol-1-yl)propyl]-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C25 H26 N2 O4
CI COM
SR CA

Absolute stereochemistry. Rotation (-).



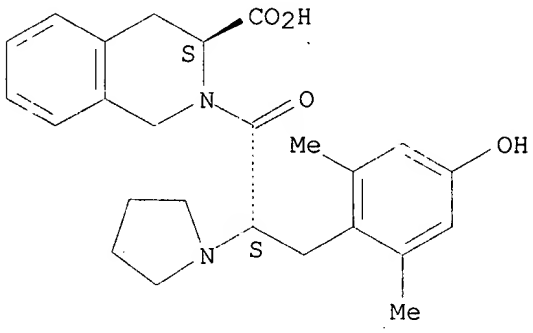
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 ANSWER 12 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 254101-71-8 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 1,2,3,4-tetrahydro-2-[(2S)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxo-2-(1-pyrrolidinyl)propyl]-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C25 H30 N2 O4 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS

CM 1

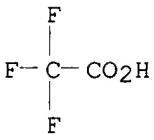
CRN 254101-70-7
CMF C25 H30 N2 O4

Absolute stereochemistry. Rotation (+).



CM 2

CRN 76-05-1
CMF C2 H F3 O2

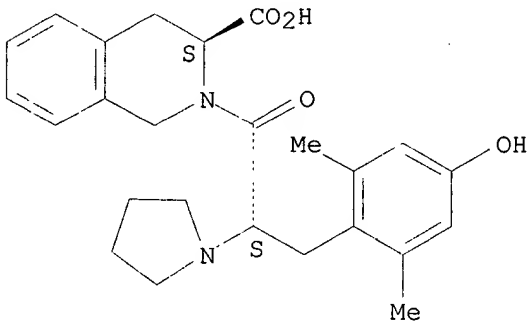


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:73213

L6 ANSWER 13 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 254101-70-7 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 1,2,3,4-tetrahydro-2-[(2S)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxo-2-(1-pyrrolidinyl)propyl]-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C25 H30 N2 O4
CI COM
SR CA

Absolute stereochemistry. Rotation (+).



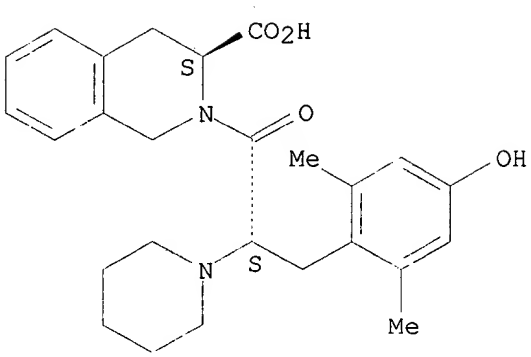
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 ANSWER 14 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 254101-69-4 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 1,2,3,4-tetrahydro-2-[(2S)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxo-2-(1-piperidinyl)propyl]-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H32 N2 O4 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS

CM 1

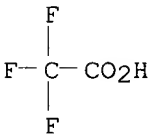
CRN 254101-68-3
CMF C26 H32 N2 O4

Absolute stereochemistry. Rotation (-).



CM 2

CRN 76-05-1
CMF C2 H F3 O2

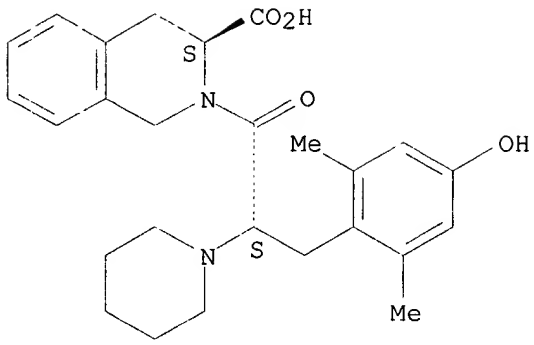


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:73213

L6 ANSWER 15 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 254101-68-3 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 1,2,3,4-tetrahydro-2-[(2S)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxo-2-(1-piperidinyl)propyl]-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H32 N2 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry. Rotation (-).



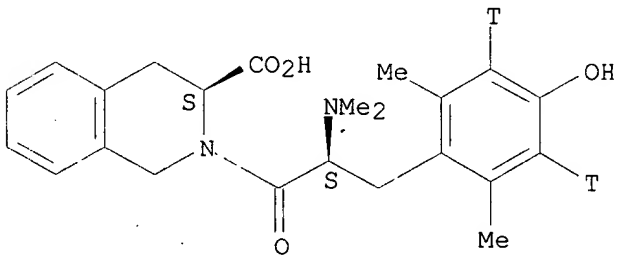
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:235885

L6 ANSWER 16 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 220045-96-5 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2S)-2-(dimethylamino)-3-(4-hydroxy-2,6-dimethylphenyl-3,5-t2)-1-oxopropyl]-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C23 H26 N2 O4 T2
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:99680

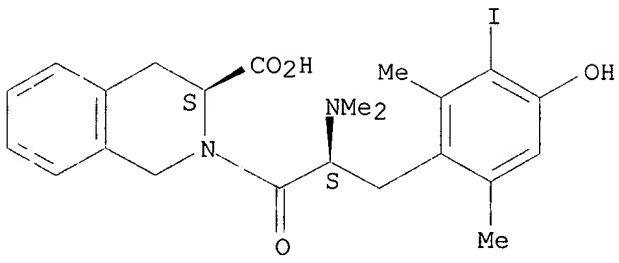
REFERENCE 2: 131:214535

REFERENCE 3: 130:139633

L6 ANSWER 17 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 220045-94-3 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2S)-2-(dimethylamino)-3-(4-hydroxy-3-iodo-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-, (3S)- (9CI)

(CA INDEX NAME)
FS STEREOSEARCH
MF C23 H27 I N2 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

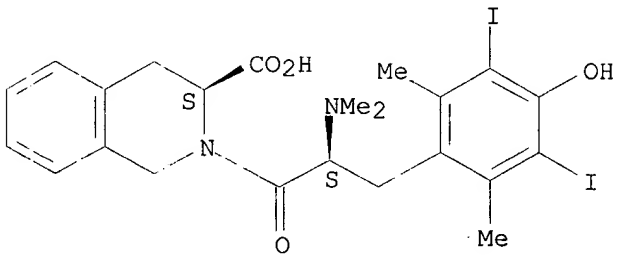
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:214535

REFERENCE 2: 130:139633

L6 ANSWER 18 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 220045-93-2 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2S)-2-(dimethylamino)-3-(4-hydroxy-3,5-diiodo-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C23 H26 I2 N2 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:99680

REFERENCE 2: 131:214535

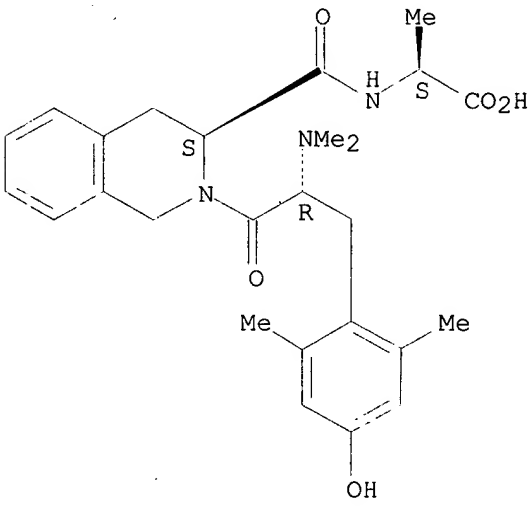
REFERENCE 3: 130:139633

L6 ANSWER 19 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 194857-76-6 REGISTRY
CN L-Alanine, N,N,2,6-tetramethyl-D-tyrosyl-(3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H33 N3 O5 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS

CM 1

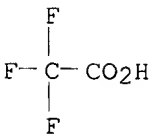
CRN 194857-75-5
CMF C26 H33 N3 O5

Absolute stereochemistry. Rotation (+).



CM 2

CRN 76-05-1
CMF C2 H F3 O2

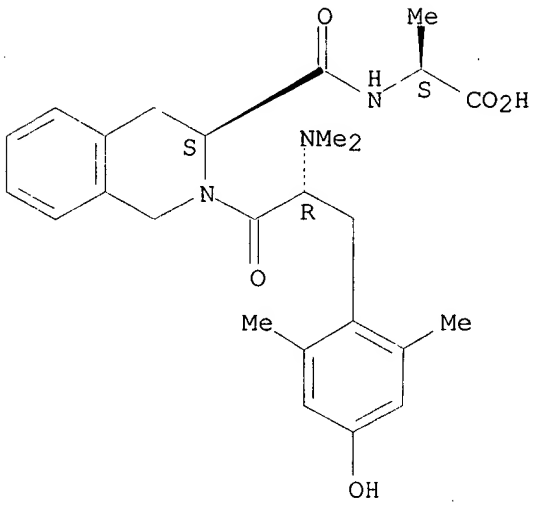


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:214595

L6 ANSWER 20 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 194857-75-5 REGISTRY
CN L-Alanine, N,N,2,6-tetramethyl-D-tyrosyl-(3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H33 N3 O5
CI COM
SR CA

Absolute stereochemistry. Rotation (+).

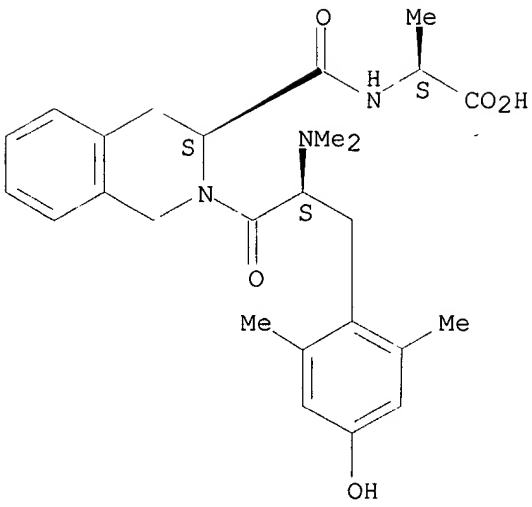


L6 ANSWER 21 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 194857-74-4 REGISTRY
CN L-Alanine, N,N,2,6-tetramethyl-L-tyrosyl-(3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H33 N3 O5 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS

CM 1

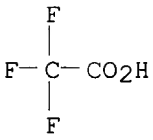
CRN 194857-73-3
CMF C26 H33 N3 O5

Absolute stereochemistry. Rotation (+).



CM 2

CRN 76-05-1
CMF C2 H F3 O2

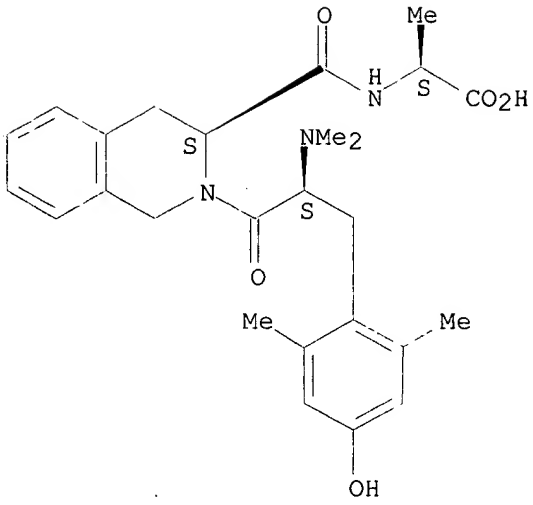


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:214595

L6 ANSWER 22 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 194857-73-3 REGISTRY
CN L-Alanine, N,N,2,6-tetramethyl-L-tyrosyl-(3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H33 N3 O5
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

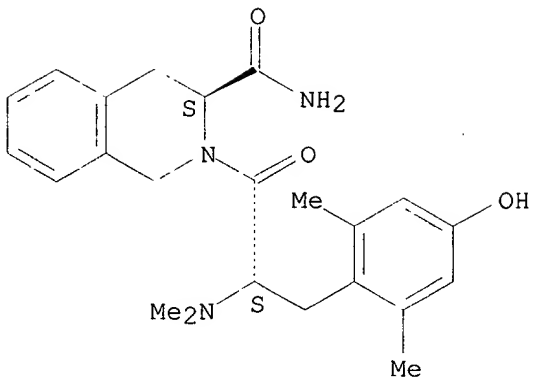
REFERENCE 1: 131:200061

L6 ANSWER 23 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 194857-72-2 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[2-(dimethylamino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-, [S-(R*,R*)]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C23 H29 N3 O3 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS

CM 1

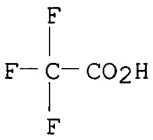
CRN 178951-50-3
CMF C23 H29 N3 O3

Absolute stereochemistry. Rotation (+).



CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

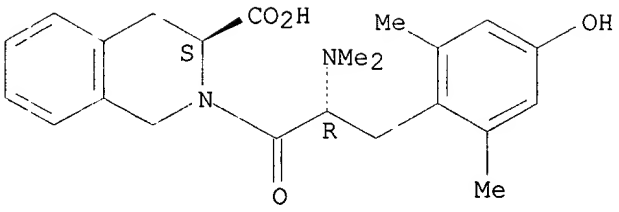
REFERENCE 1: 127:214595

L6 ANSWER 24 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 194857-71-1 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[2-(dimethylamino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-, [S-(R*,S*)]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C23 H28 N2 O4 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS

CM 1

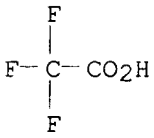
CRN 194857-70-0
CMF C23 H28 N2 O4

Absolute stereochemistry. Rotation (+).



CM 2

CRN 76-05-1
CMF C2 H F3 O2

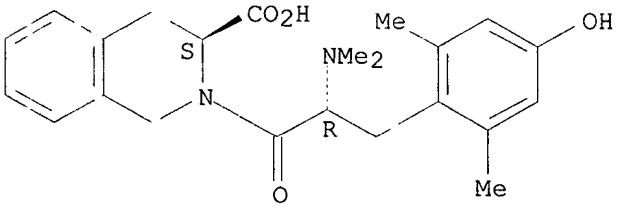


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:214595

L6 ANSWER 25 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 194857-70-0 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2R)-2-(dimethylamino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Isoquinolinecarboxylic acid, 2-[2-(dimethylamino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-, [S-(R*,S*)]-
FS STEREOSEARCH
MF C23 H28 N2 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

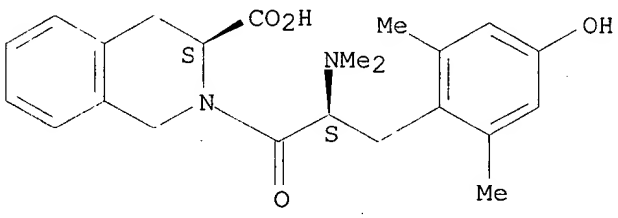
REFERENCE 1: 131:200061

L6 ANSWER 26 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 194857-69-7 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[2-(dimethylamino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-, [S-(R*,R*)]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C23 H28 N2 O4 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS

CM 1

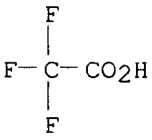
CRN 178951-49-0
CMF C23 H28 N2 O4

Absolute stereochemistry. Rotation (+).



CM 2

CRN 76-05-1
CMF C2 H F3 O2



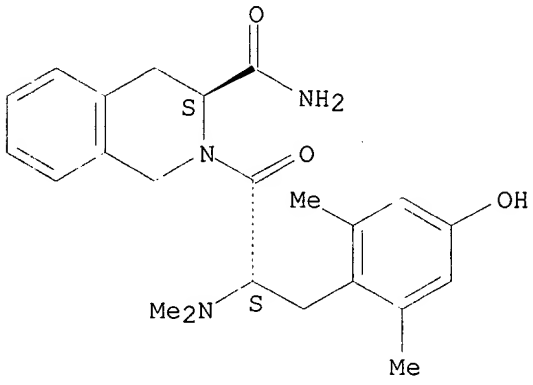
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:214595

L6 ANSWER 27 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 178951-50-3 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-(dimethylamino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Isoquinolinecarboxamide, 2-[2-(dimethylamino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-, [S-(R*,R*)]-

FS STEREOSEARCH
MF C23 H29 N3 O3
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

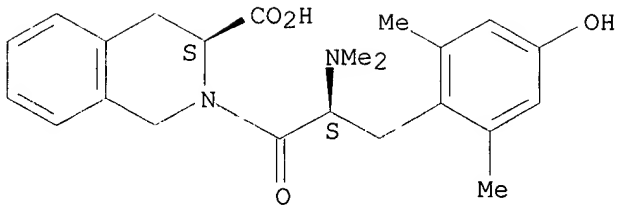
REFERENCE 1: 134:51294

REFERENCE 2: 131:200061

REFERENCE 3: 125:105145

L6 ANSWER 28 OF 28 REGISTRY COPYRIGHT 2002 ACS
RN 178951-49-0 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2S)-2-(dimethylamino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Isoquinolinecarboxylic acid, 2-[2-(dimethylamino)-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-, [S-(R*,R*)]-
FS STEREOSEARCH
MF C23 H28 N2 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

8 REFERENCES IN FILE CA (1967 TO DATE)
8 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:352508

REFERENCE 2: 135:235885

REFERENCE 3: 134:66089

REFERENCE 4: 132:73213

REFERENCE 5: 131:214535

REFERENCE 6: 131:200061

REFERENCE 7: 130:139633

REFERENCE 8: 125:105145

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=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 19:12:30 ON 02 APR 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 2 Apr 2002  VOL 136 ISS 14
FILE LAST UPDATED: 31 Mar 2002  (20020331/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

CAS roles have been modified effective December 16, 2001. Please
check your SDI profiles to see if they need to be revised. For
information on CAS roles, enter HELP ROLES at an arrow prompt or use
the CAS Roles thesaurus (/RL field) in this file.

The P indicator for Preparations was not generated for all of the
CAS Registry Numbers that were added to the CAS files between 12/27/01
and 1/23/02.  As of 1/23/02, the situation has been resolved.  Searches
and/or SDIs in the H/Z/CA/CAplus files incorporating CAS Registry
Numbers with the P indicator executed between 12/27/01 and 1/23/02 may
be incomplete.  See the NEWS message on this topic for more information.

=>
=>

=> d stat que l10
L1                STR
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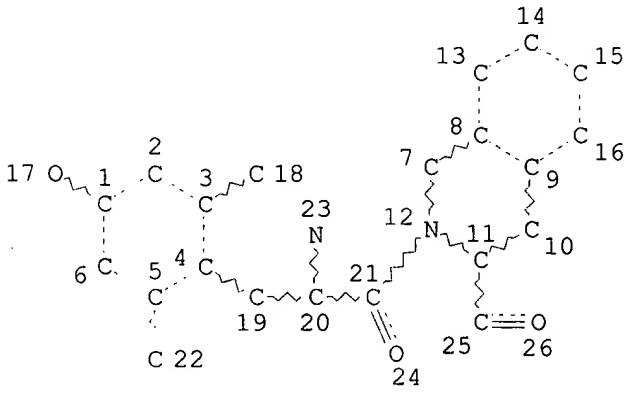


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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 26

STEREO ATTRIBUTES: NONE
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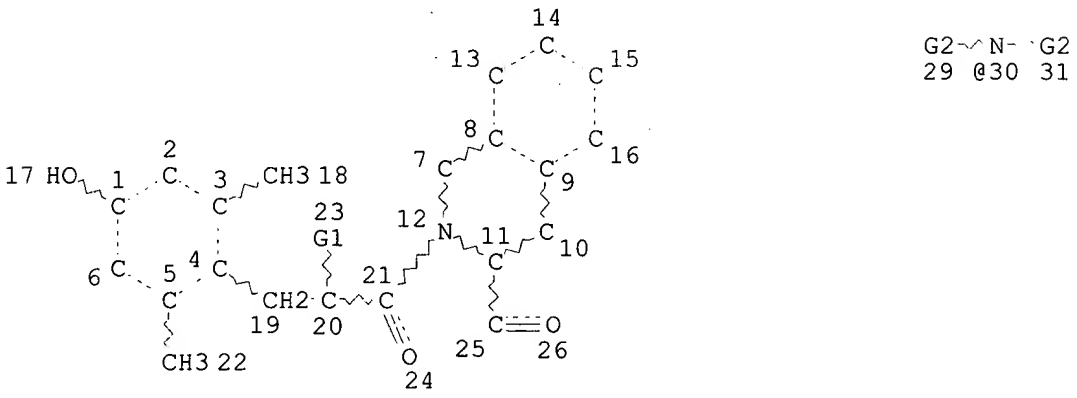
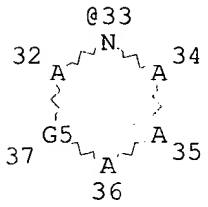
L5 STR





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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 35

STEREO ATTRIBUTES: NONE
L6 28 SEA FILE=REGISTRY SUB=L3 SSS FUL L5
L7 11 SEA FILE=HCAPLUS ABB=ON PLU=ON L6
L9 174 SEA FILE=REGISTRY ABB=ON PLU=ON L3 NOT L6
L10 28 SEA FILE=HCAPLUS ABB=ON PLU=ON L9 NOT L7

=>
=>

=> d ibib abs hitrn l10 1-28

L10 ANSWER 1 OF 28 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:14209 HCAPLUS
TITLE: Evaluation of the Dmt-Tic Pharmacophore: Conversion of a Potent .delta.-Opioid Receptor Antagonist into a Potent .delta. Agonist and Ligands with Mixed Properties
AUTHOR(S): Balboni, Gianfranco; Guerrini, Remo; Salvadori, Severo; Bianchi, Clementina; Rizzi, Daniela; Bryant, Sharon D.; Lazarus, Lawrence H.
CORPORATE SOURCE: Department of Toxicology, University of Cagliari, Cagliari, 09126, Italy
SOURCE: Journal of Medicinal Chemistry (2002), 45(3), 713-720
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Analogs of the 2',6'-dimethyl-L-tyrosine (Dmt)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) pharmacophore were prepd. to test the hypothesis that a "spacer" and a third arom. center in opioid peptides are required to convert a .delta.-antagonist into ligands with .delta.-agonist or with mixed .delta.-antagonist/.mu.-agonist properties. Potent .delta.-agonists and bifunctional compds. with high .delta.- and .mu.-opioid receptor affinities were obtained by varying the spacer length [none, NH-CH2, NH-CH2-CH2, Gly-NH-CH2] and C-terminal arom. nucleus [1H-benzimidazole-2-yl, Ph and benzyl groups]. C-terminal modification primarily affected .mu.-opioid receptor affinities, which increased maximally 1700-fold relative to the prototype .delta.-antagonist H-Dmt-Tic-NH2 and differentially modified bioactivity. In the absence of a spacer (1), the analog exhibited dual .delta.-agonism (pEC50, 7.28) and .delta.-antagonism (pA2, 7.90). H-Dmt-Tic-NH-CH2-1H-benzimidazol-2-yl (Bid) (2) became a highly potent .delta.-agonist (pEC50, 9.90), slightly greater than deltorphin C (pEC50, 9.56), with .mu.-agonism (pE50, 7.57), while H-Dmt-Tic-Gly-NH-CH2-Bid (4) retained potent .delta.-antagonism (pA2, 9.0) but with an order of magnitude less .mu.-agonism. Similarly, H-Dmt-Tic-Gly-NH-Ph (5) had nearly equiv. high .delta.-agonism (pEC50, 8.52) and .mu.-agonism (pEC50, 8.59), while H-Dmt-Tic-Gly-NH-CH2-Ph (6) whose spacer was longer by a single methylene group exhibited potent .delta.-antagonism (pA2, 9.25) and very high .mu.-agonism (pEC50, 8.57). These data confirm that the distance between the Dmt-Tic pharmacophore and a third arom. nucleus is an important criterion in converting Dmt-Tic from a highly potent .delta.-antagonist into a potent .delta.-agonist or into ligands with mixed .delta.- and .mu.-opioid properties.

IT **403652-10-8P 403652-11-9P 403652-12-0P**
403652-13-1P 403652-14-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(evaluation of Dmt-Tic pharmacophore: conversion of a potent .delta.-opioid receptor antagonist into a potent .delta. agonist and ligands with mixed properties)

IT **403652-17-5P 403652-21-1P 403652-25-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(evaluation of Dmt-Tic pharmacophore: conversion of a potent .delta.-opioid receptor antagonist into a potent .delta. agonist and ligands with mixed properties)

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:321139 HCAPLUS

DOCUMENT NUMBER: 135:92838
TITLE: A convenient synthesis of N-Fmoc-N,N'-bis-Boc-7-guanyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Fmoc-N,N'-bis-Boc-7-guanyl-Tic-OH, GTIC)
AUTHOR(S): Santagada, V.; Fiorino, F.; Severino, B.; Salvadori, S.; Lazarus, L. H.; Bryant, S. D.; Caliendo, G.
CORPORATE SOURCE: Dipartimento di Chimica Farmaceutica e Tossicologica, Universita di Napoli, 'Federico II', Naples, 80131, Italy
SOURCE: Tetrahedron Letters (2001), 42(20), 3507-3509
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 135:92838
AB Fmoc-N,N'-Bis-Boc-7-guanyl-Tic-OH (GTIC), a conformationally constrained amino acid with basic properties, has been synthesized in four steps. This amino acid can be incorporated into peptides using std. Fmoc solid phase synthesis, and to test its potential for biol. activity applications, we prepd. an analog of H-Dmt-Tic-NH2.
IT **349151-65-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis of protected guanyltetrahydroisoquinolinecarboxylic acid (GTIC) and biol. activity of dipeptide contg. GTIC)
IT **349151-66-2P 349151-67-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of protected guanyltetrahydroisoquinolinecarboxylic acid (GTIC) and biol. activity of dipeptide contg. GTIC)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:894623 HCAPLUS
DOCUMENT NUMBER: 135:40848
TITLE: Opioid dipeptide derivatives with a mixed .mu. agonist/.delta. antagonist, partial .mu. agonist/.delta. antagonist or .mu. agonist/partial .delta. agonist profile
AUTHOR(S): Schiller, Peter W.; Weltrowska, Grazyna; Nguyen, Thi M. -D.; Wilkes, Brian C.; Lemieux, Carole; Chung, Nga N.
CORPORATE SOURCE: Laboratory of Chemical Biology and Peptide Research, Clinical Research Institute of Montreal, Montreal, QC, H2W 1R7, Can.
SOURCE: Peptides for the New Millennium, Proceedings of the American Peptide Symposium, 16th, Minneapolis, MN, United States, June 26-July 1, 1999 (2000), Meeting Date 1999, 229-230. Editor(s): Fields, Gregg B.; Tam, James P.; Barany, George. Kluwer Academic Publishers: Dordrecht, Neth.
CODEN: 69ATHX
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Opioid compds. with a mixed .mu. agonist/.delta. antagonist profile are expected to be analgesics with low propensity to produce tolerance and dependence. The first fully characterized mixed .mu. agonist/.delta.

antagonist was the pseudotetrapeptide H-Dmt-Tic[CH2NH]Phe-Phe-NH2; Dmt = 2',6'-dimethyltyrosine which produced a potent analgesic effect, no dependence and less tolerance than morphine. In an effort to develop mixed .mu. agonist/.delta. antagonists of lower mol. wt. capable of crossing the blood-brain barrier, dipeptide derivs. of the general formula H-Xxx-Tic-NH-R, where Xxx is tyrosine or a tyrosine analog and R represents an aralkyl or alkyl substituent, were synthesized. The dipeptide derivs. were synthesized in soln. using the mixed anhydride method. In vitro opioid agonist or antagonist activities of the resulting compds. were detd. in the .mu. receptor-representative guine pig ileum assay and in the .delta. receptor-representative mouse vas deferens assay, and their .mu., .delta., .kappa. opioid receptor affinities were measured in binding assays based on the displacement of .mu.-, .delta.- and .kappa.-selective radioligands from rat or guinea pig brain membrane binding sites.

IT **173927-99-6P 209786-77-6P 344615-76-5P**
344615-77-6P 344615-78-7P 344615-79-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(opioid dipeptide derivs. with mixed .mu. agonist/.delta. antagonist, partial .mu. agonist/.delta. antagonist or .mu. agonist/partial .delta. agonist profile)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:853641 HCAPLUS
DOCUMENT NUMBER: 134:216792
TITLE: Assessment of substitution in the second pharmacophore of Dmt-Tic analogues
AUTHOR(S): Santagada, V.; Balboni, G.; Caliendo, G.; Guerrini, R.; Salvadori, S.; Bianchi, C.; Bryant, S. D.; Lazarus, L. H.
CORPORATE SOURCE: Medicinal Chemistry and Toxicology, University of Naples, Naples, I-80134, Italy
SOURCE: Bioorganic & Medicinal Chemistry Letters (2000), 10(24), 2745-2748
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The Dmt-Tic pharmacophore exhibits potent .delta.-opioid receptor antagonism. Analogs with substitutions in the second pharmacophore with or without a COOH function were synthesized: several had high .delta. affinity, but exhibited low to non-selectivity toward .mu. receptors similar to H-Dmt-Tic-amide and H-Dmt-Tic-ol. Functional bioactivity indicated high .delta. antagonism (pA2 7.4-7.9) and modest .mu. agonism, pEC50 (6.1-6.3), but with Emax values analogous to dermorphin. These Dmt-Tic analogs with mixed .delta. antagonist/.mu. agonist properties would appear to be better candidates as analgesics than pure .mu. agonists.

IT **329320-07-2**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(opioid receptor binding activity of dimethyltyrosine isoquinolinecarboxylates)

IT **329319-96-2P 329320-05-0P**

RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(opioid receptor binding activity of dimethyltyrosine isoquinolinecarboxylates)
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:288696 HCAPLUS
DOCUMENT NUMBER: 133:12871
TITLE: Opioid peptide analogs containing 2'-hydroxy,6'-methyltyrosine in place of Tyr1 display greatly enhanced .delta. antagonist potency but unchanged .mu. agonist potency
AUTHOR(S): Berezowska, Irena; Lemieux, Carole; Nguyen, Thi M. -D.; Chung, Nga N.; Schiller, Peter W.
CORPORATE SOURCE: Clinical Research Institute of Montreal, Montreal, QC, H2W 1R7, Can.
SOURCE: Peptides 1998, Proceedings of the European Peptide Symposium, 25th, Budapest, Aug. 30-Sept. 4, 1998 (1999), Meeting Date 1998, 718-719. Editor(s): Bajusz, Sandor; Hudecz, Ferenc. Akademiai Kiado: Budapest, Hung.
CODEN: 68WKAY
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The authors report the syntheses and in vitro opioid activity profiles of the Hmt1-analogs of the .delta. antagonists TIP (H-Tyr-Tic-Phe-OH) and TIPP (H-Tyr-Tic-Phe-Phe-OH) and of the .mu. agonists TAPP (H-Tyr-D-Ala-Phe-Phe-NH2) and DALDA (H-Tyr-D-Arg-Phe-Lys-NH2). In vitro opioid activities of the compds. were detd. in the .mu.-receptor-representative guinea pig ileum assay and in the .delta. receptor-representative mouse vas deferens (MVD) assay, and their .mu. and .delta. receptor affinities were measured in binding assays based on displacement of [3H]DAMGO and [3H]DSLET, resp., from rat brain membrane binding sites. The tripeptide H-Hmt-Tic-Phe-OH was an about 15 times more potent .delta. antagonist against the .delta. agonist DPDPE than its parent TIP, showing .delta. antagonist potency (MVD) and .delta. receptor binding affinity in the subnanomolar range. Furthermore, this compd. showed greatly improved .delta. receptor selectivity as compared to TIP. The Hmt1-analog of the tetrapeptide TIPP, H-Hmt-Tic-Phe-Phe-OH, displayed very high .delta. antagonist potency in the MVD assay, comparable to that of H-Dmt-Tic-Phe-Phe-OH. In the binding assays, it showed slightly higher .delta. receptor affinity than H-Dmt-Tic-Phe-Phe-OH and 20-fold higher .delta. selectivity. Thus, [Hmt1]TIPP ranks among the most potent and most specific .delta. opioid antagonists reported to date. Substitution of Hmt for Tyr1 in the .mu. agonist peptides TAPP and DALDA resulted in .mu.-agonist potencies comparable to those of their resp. parent peptides,. In conclusion, replacement of Tyr1 in opioid peptides with Hmt produced a potency increase in the case of the .delta. antagonists but not in the case of the .mu. agonists.
IT **156219-37-3**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(opioid peptide analogs .delta. antagonist and .mu. agonist activity in relation to structure)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:94013 HCAPLUS
DOCUMENT NUMBER: 132:245845
TITLE: Novel Dmt-Tic dipeptide analogues as selective delta-opioid receptor antagonists
AUTHOR(S): Page, D.; McClory, A.; Mischki, T.; Schmidt, R.; Butterworth, J.; St-Onge, S.; Labarre, M.; Payza, K.; Brown, W.
CORPORATE SOURCE: Department of Chemistry, AstraZeneca R and D Montreal, Saint-Laurent, PQ, H4S 1Z9, Can.
SOURCE: Bioorg. Med. Chem. Lett. (2000), 10(2), 167-170
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of Dmt-Tic analogs with substitution on the Tic arom. ring has been synthesized and evaluated for opioid receptor affinity and activation. Incorporation of large hydrophobic groups at position 7 of Tic did not greatly alter the .delta. opioid receptor binding affinities of the dipeptides whereas substitution at position 6 substantially diminished their affinity. These modified Dmt-Tic peptides showed binding affinities as low as 2.5 nM with .ltoreq.500-fold selectivity for the .delta. vs. .mu. opioid receptor and proved to be .delta. receptor antagonists.
IT **262616-34-2P 262616-35-3P 262616-36-4P**
262616-37-5P 262616-38-6P 262616-39-7P
262616-40-0P 262616-41-1P 262616-42-2P
262616-43-3P 262616-44-4P 262616-45-5P
262616-46-6P 262616-47-7P 262616-48-8P
262616-49-9P 262616-50-2P 262616-51-3P
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(novel Dmt-Tic dipeptide analogs as selective delta-opioid receptor antagonists)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 7 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:667719 HCAPLUS
DOCUMENT NUMBER: 131:347049
TITLE: (2S,3R)TMT-L-Tic-OH is a potent inverse agonist at the human .delta.-opioid receptor
AUTHOR(S): Hosohata, Keiko; Burkey, Thomas H.; Alfaro-Lopez, Josua; Hruby, Victor J.; Roeske, William R.; Yamamura, Henry I.
CORPORATE SOURCE: Departments of Pharmacology, Biochemistry, Psychiatry and Chemistry, University of Arizona, Tucson, AZ, 85724, USA
SOURCE: Eur. J. Pharmacol. (1999), 380(1), R9-R10
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We examd. the pharmacol. effect of .beta.-methyl-2',6'-dimethyltyrosine-L-tetrahydroisoquinoline-3-carboxylic acid ((2S,3R)TMT-L-Tic-OH) on G protein activation in membranes prepd. from Chinese Hamster Ovary cells transfected with cDNA of the human .delta.-opioid receptor.

(2S,3R)TMT-L-Tic-OH inhibited G protein activation to 58% of basal with an EC50 of 0.72 nM as detd. by [35S]GTP.gamma.S binding. These findings suggest that (2S,3R)TMT-L-Tic-OH is a highly potent inverse agonist at the human .delta.-opioid receptor.

IT **250331-76-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
((2S,3R)TMT-L-Tic-OH is a potent inverse agonist at the human .delta.-opioid receptor)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:484863 HCAPLUS
DOCUMENT NUMBER: 131:266894
TITLE: The Opioid .mu. Agonist/.delta. Antagonist DIPP-NH2[.PSI.] Produces a Potent Analgesic Effect, No Physical Dependence, and Less Tolerance than Morphine in Rats
AUTHOR(S): Schiller, Peter W.; Fundytus, Marian E.; Merovitz, Lisa; Weltrowska, Grazyna; Nguyen, Thi M.-D.; Lemieux, Carole; Chung, Nga N.; Coderre, Terence J.
CORPORATE SOURCE: Laboratory of Chemical Biology and Peptide Research and Pain Mechanisms Laboratory, Clinical Research Institute of Montreal, Montreal, PQ, H2W 1R7, Can.
SOURCE: J. Med. Chem. (1999), 42(18), 3520-3526
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Opioid compds. with mixed .mu. agonist/.delta. antagonist properties are expected to be analgesics with low propensity to produce tolerance and dependence. In an effort to strengthen the .mu. agonist component of the mixed .mu. agonist/.delta. antagonist H-Tyr-Tic-Phe-Phe-NH2 (TIPP-NH2), analogs contg. structurally modified tyrosine residues in place of Tyr1 were synthesized. Among the prepd. compds., H-Dmt-Tic-Phe-Phe-NH2 (DIPP-NH2; Dmt = 2',6'-dimethyltyrosine) and H-Dmt-Tic.PSI.[CH2NH]Phe-Phe-NH2 (DIPP-NH2[.PSI.]) retained a mixed .mu. agonist/.delta. antagonist profile, as detd. in the guinea pig ileum and mouse vas deferens assays, whereas H-Tmt-Tic-Phe-Phe-NH2 (Tmt = N,2',6'-trimethyltyrosine) was a partial .mu. agonist/.delta. antagonist and H-Tmt-Tic.PSI.[CH2NH]Phe-Phe-NH2 was a .mu. antagonist/.delta. antagonist. DIPP-NH2[.PSI.] showed binding affinities in the subnanomolar range for both .mu. and .delta. receptors in the rat brain membrane binding assays, thus representing the first example of a balanced .mu. agonist/.delta. antagonist with high potency. In the rat tail flick test, DIPP-NH2[.PSI.] given icv produced a potent analgesic effect (ED50 = 0.04 .mu.g), being about 3 times more potent than morphine (ED50 = 0.11 .mu.g). It produced less acute tolerance than morphine but still a certain level of chronic tolerance. Unlike morphine, DIPP-NH2[.PSI.] produced no phys. dependence whatsoever upon chronic administration at high doses (.ltoreq.4.5 .mu.g/h) over a 7-day period. In conclusion, DIPP-NH2[.PSI.] fulfills to a large extent the expectations based on the mixed .mu. agonist/.delta. antagonist concept with regard to analgesic activity and the development of tolerance and dependence.

IT **160429-67-4P 245538-28-7P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

(opioid .mu. agonist/.delta. antagonist DIPP-NH2[.PSI.] produces a potent analgesic effect and No phys. dependence and less tolerance than morphine in Rats in relation to structure)
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:396632 HCAPLUS
DOCUMENT NUMBER: 131:208606
TITLE: A new class of dipeptide derivatives that are potent and selective .delta. opioid agonists
AUTHOR(S): Schiller, P. W.; Weltrowska, G.; Berezowska, I.; Lemieux, C.; Chung, N. N.; Carpenter, K. A.; Wilkes, B. C.
CORPORATE SOURCE: Clinical Research Institute of Montreal, Montreal, PQ, H2W 1R7, Can.
SOURCE: Pept. Proc. Am. Pept. Symp., 15th (1999), Meeting Date 1997, 514-516. Editor(s): Tam, James P.; Kaumaya, Pravin T. P. Kluwer: Dordrecht, Neth.
CODEN: 67UCAR
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A new class of potent and selective .delta.-opioid agonists has been developed by alteration of dipeptides having the general formula H-Tyr-Tic-NH-(CH2)n-Ph. Structure-activity data are presented for 18 dipeptides (displacement of DAMGO vs. DSLET from rat brain membrane binding sites).
IT **209786-77-6 209786-79-8**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dipeptide derivs. that are potent and selective .delta. opioid agonists)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 10 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:597921 HCAPLUS
DOCUMENT NUMBER: 129:339945
TITLE: Subtleties of structure-.delta. agonist vs. .delta. antagonist relationships of opioid dipeptide derivatives
AUTHOR(S): Schiller, P. W.; Weltrowska, G.; Bolewska-Pedyczak, E.; Nguyen, T. M-D.; Lemieux, C.; Chung, N. N.
CORPORATE SOURCE: Laboratory of Chemical Biology and Peptide Research, Clinical Research Institute of Montreal, Montreal, PQ, H2W 1R7, Can.
SOURCE: Pept. 1996, Proc. Eur. Pept. Symp., 24th (1998), Meeting Date 1996, 785-786. Editor(s): Ramage, Robert; Epton, Roger. Mayflower Scientific: Kingswinford, UK.
CODEN: 66RCA5
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Recently, the authors reported that the dipeptide deriv. H-Tyr-Tic-NH-(Ch2)2-Ph represents a new prototype of a moderately potent .delta.-selective opioid agonist. In the present paper, the authors describe how subtle structural modifications of this parent structure led to a potent and selective .delta. agonist, .delta. antagonists and mixed .mu. agonist/.delta. antagonists. Compds. were synthesized by soln.

methods and their opioid activity profiles were detd. in vitro in the guinea pig ileum and mouse vas deferens bioassays and the rat brain membrane receptor binding assays.

IT **215596-98-8 215597-26-5 215597-37-8**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(subtleties of structure-.delta. agonist vs. .delta. antagonist relationships of opioid dipeptide derivs.)

L10 ANSWER 11 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:507698 HCAPLUS
DOCUMENT NUMBER: 129:245476
TITLE: Conformationally constrained opioid peptide analogs with novel activity profiles
AUTHOR(S): Schiller, Peter W.; Schmidt, Ralf; Weltrowska, Grazyna; Berezowska, Irena; Nguyen, Thi M.-D.; Dupuis, Sebastien; Chung, Nga N.; Lemieux, Carole; Wilkes, Brian C.; Carpenter, Katharine A.
CORPORATE SOURCE: Laboratory of Chemical Biology and Peptide Research, Clinical Research Institute of Montreal, Montreal, PQ, H2W 1R7, Can.
SOURCE: Lett. Pept. Sci. (1998), 5(2-3), 209-214
CODEN: LPSCEM; ISSN: 0929-5666
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Novel conformationally constrained opioid peptide analogs, having properties as .delta. antagonist, mixed .mu. agonist/.delta. antagonist or .delta. agonist, were developed. TIP(P)-related .delta. antagonists showed unprecedented .delta. antagonist potency and .delta. receptor selectivity, and may have potential for use in analgesia in combination with .mu. agonists. A definitive model of their .delta. receptor-bound conformation was developed. Three prototype mixed .mu. agonist/.delta. antagonists were discovered. They represent the only known compds. with this pharmacol. profile and, as expected, one of them was shown to be a potent analgesic and to produce no dependence and less tolerance than morphine. Novel dipeptide derivs. turned out to be potent and selective .delta. agonists. Because of their low mol. wt. and lipophilic character, these compds. may cross the blood-brain barrier and, thus, may have potential as centrally acting analgesics.

IT **156219-37-3 160429-67-4 172262-39-4 173927-99-6**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(activity profiles of conformationally constrained opioid peptide analogs)

L10 ANSWER 12 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:479553 HCAPLUS
DOCUMENT NUMBER: 129:95725
TITLE: Preparation of dipeptide derivatives for treatment of pain
INVENTOR(S): Schiller, Peter
PATENT ASSIGNEE(S): Astra AB (Publ), Swed.
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

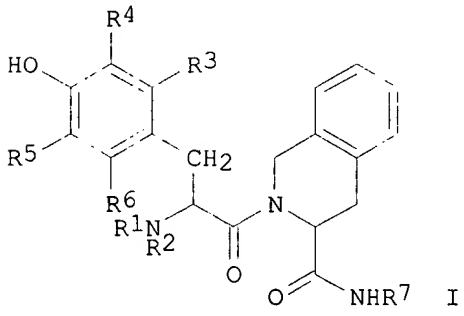
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9828327	A1	19980702	WO 1997-SE2156	19971218
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9855808	A1	19980717	AU 1998-55808	19971218
AU 721131	B2	20000622		
EP 946588	A1	19991006	EP 1997-952145	19971218
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001507026	T2	20010529	JP 1998-528696	19971218
US 6150335	A	20001121	US 1998-43881	19980401
NO 9903069	A	19990621	NO 1999-3069	19990621

PRIORITY APPLN. INFO.: SE 1996-4789 A 19961220
WO 1997-SE2156 W 19971218

OTHER SOURCE(S): MARPAT 129:95725

GI



I

AB Dipeptide derivs. I [R1, R2 = independently H, Me(CH2)n, Ph(CH2)m, cyclopropylmethyl, allyl; R3-R6 = H; R3 = C1-6 alkyl, R4-R6 = H; R3 = R6 = C1-6 alkyl, R4 = R5 = H; R3 = R5 = R6 = H, R4 = F, Cl, Br, iodo, OH, NO2, NH2; R7 = (un)substituted 2-phenylethyl or 2-cyclohexylethyl; n = 0-12; m = 1-3] are claimed for the manuf. of a medicament for the treatment of pain. The compds. are .delta. opioid agonists and thus useful in the treatment of pain without the requirement of co-application of a .mu. opioid agonist. Thus, amidation of Boc-Tic-OH (Boc = Me3CO2C; Tic = L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid) with 2,2-diphenylethylamine, deprotection, peptide coupling with Boc-Tyr(Boc)-OH, and final deprotection gave desired dipeptide deriv. H-Tyr-Tic-NHCH2CHPh2 (II). II and related dipeptide derivs. are selective .delta. opioid agonists, with II having Ki = 0.981 nM in a .delta. opioid receptor assay.

IT **209786-71-0P 209786-77-6P 209786-79-8P**
209786-80-1P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP

(Preparation); USES (Uses)
(prepn. of dipeptide derivs. for treatment of pain)

L10 ANSWER 13 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:102445 HCAPLUS
DOCUMENT NUMBER: 128:226374
TITLE: Rational design of dynorphin A analogs with .delta.-receptor selectivity and antagonism for .delta.- and .kappa.-receptors
AUTHOR(S): Guerrini, Remo; Capasso, Anna; Marastoni, Mauro; Bryant, Sharon D.; Cooper, Peter S.; Lazarus, Lawrence H.; Temussi, Piero A.; Salvadori, Severo
CORPORATE SOURCE: Department of Pharmaceutical Sciences and Biotechnology Center, University of Ferrara, Ferrara, I-44100, Italy
SOURCE: Bioorg. Med. Chem. (1998), 6(1), 57-62
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Substitution of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) in place of Gly2 in dynorphin A-(1-13)-NH2 and -(1-11)-NH2 (DYN) analogs (1 and 2) decreased the affinity to the .kappa., .delta., and .mu. receptors, and .kappa. selectivity. The analog [D-Ala2, des-Gly3]DYN (4), a chimera between deltorphin/dermorphin N-terminal tripeptide and DYN, was virtually inactive for .kappa.-sites while the affinities for .delta.- and .mu.-receptors remained essentially unchanged. The doubly substituted analog [2',6'-dimethyl-L-tyrosine (Dmt1)-Tic2]DYN (3) exhibited high .delta.-affinity (Ki=0.39 nM) while .mu.- and .kappa.-affinities were only an order of magnitude less (4-5 nM). Bioactivity of [Tic2]DYN peptides (1-3) on guinea-pig ileum and rabbit jejunum revealed potent .delta.- and .kappa.-antagonism, while the .delta. agonist potency of 4 was comparable to DYN. Thus, conversion from a .kappa.-agonist to antagonist occurred with the inclusion of Tic into DYN analogs, similar to the appearance of antagonist properties with .delta.- and .mu.-opioid agonists contg. a Tic2 residue.
IT **204764-01-2P**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(rational design of dynorphin A analogs with .delta.-receptor selectivity and antagonism for .delta.- and .kappa.-receptors)

L10 ANSWER 14 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:20189 HCAPLUS
DOCUMENT NUMBER: 128:162532
TITLE: The stereochemical requirements of the novel .delta.-opioid selective dipeptide antagonist TMT-TIC
AUTHOR(S): Liao, Subo; Lin, Jun; Shenderovich, Mark D.; Han, Yinglin; Hasohata, Keiko; Davis, Peg; Qiu, Wei; Porreca, Frank; Yamamura, Henry I.; Hruby, Victor J.
CORPORATE SOURCE: Department of Chemistry, The University of Arizona, Tucson, AZ, 85721, USA
SOURCE: Bioorg. Med. Chem. Lett. (1997), 7(23), 3049-3052
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Five conformationally constrained dipeptide TMT-L-Tic analogs have been

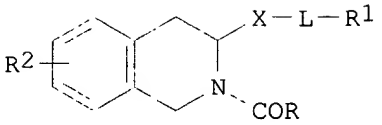
synthesized and evaluated for their bioactivity using in vitro bioassays. The most potent and selective analog (2S,3R)-TMT-L-Tic showed 9 nM binding affinity and 4000-fold selectivity for the .delta. vs. .mu. opioid receptor. The lowest-energy conformation of (2S,3R)-TMT-L-Tic is suggested to be bioactive one in which the .chi.1 torsional angle is trans for TMT and gauche (+) for Tic.

IT **202860-53-5P 202860-54-6P 202860-55-7P**
202860-56-8P 202860-57-9P
RL: BPR (Biological process); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(stereochem. requirements of the novel .delta.-opioid selective dipeptide antagonist TMT-TIC)

L10 ANSWER 15 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:594750 HCAPLUS
DOCUMENT NUMBER: 127:248425
TITLE: Isoquinolines useful as analgesics
INVENTOR(S): Dimaio, John; Wang, Wuyi
PATENT ASSIGNEE(S): Astra AB, Swed.; Dimaio, John; Wang, Wuyi
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9731940	A1	19970904	WO 1997-SE315	19970225
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2244219	AA	19970904	CA 1997-2244219	19970225
AU 9721090	A1	19970916	AU 1997-21090	19970225
AU 722032	B2	20000720		
CN 1211990	A	19990324	CN 1997-192558	19970225
EP 914332	A1	19990512	EP 1997-906381	19970225
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9707767	A	19990727	BR 1997-7767	19970225
JP 2000506138	T2	20000523	JP 1997-530865	19970225
US 6034097	A	20000307	US 1997-930867	19971006
NO 9803945	A	19981006	NO 1998-3945	19980827

PRIORITY APPLN. INFO.: SE 1996-769 A 19960228
WO 1997-SE315 W 19970225
OTHER SOURCE(S): MARPAT 127:248425
GI



I

AB Peptidomimetic isoquinolines I [X = CH2NHCO, CH2NHCO2, CONH, CH2NH; L = (un)substituted alkyl; R = 3-aryl- or 3-aralkyl-2-pyrrolidinyl or -2-piperidinyl, 1-[(un)substituted amino]alkyl or -aralkyl; R1 = aryl, aralkyl, alkyl; R2 = alkyl, H, OH, halo, SH, NO2, NH2, alkylamino, NH:C(NH2), NH:C(NH2)NH, CO2H or carbalkoxy] were prepd. as analgesics. Thus, 2-[2-guanidino-3-(4-hydroxy-2,6-dimethylphenyl)propionyl]-1,2,3,4-tetrahydroisoquinoline-3-S-carboxylic acid (2-R-hydroxy-3-phenylpropyl)amide bistrifluoroacetate was prepd. and assayed for analgesic activity (Ki.mu. = 2.03.+-.0.37, Ki.delta. = 0.56.+-.0.09, and Ki.kappa. = 276.6.+-.13.6 nM).

IT **195831-57-3P 195831-71-1P 195831-73-3P 195831-77-7P 195831-82-4P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(isoquinolines useful as analgesics)

IT **195832-13-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(isoquinolines useful as analgesics)

IT **195831-53-9P 195831-55-1P 195831-59-5P 195831-61-9P 195831-63-1P 195831-65-3P 195831-67-5P 195831-69-7P 195831-75-5P 195831-78-8P 195831-80-2P 195831-84-6P 195831-86-8P 195831-88-0P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(isoquinolines useful as analgesics)

L10 ANSWER 16 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:455179 HCAPLUS
DOCUMENT NUMBER: 127:171672
TITLE: Design and solution structure of a partially rigid opioid antagonist lacking the basic center. Models of antagonism
AUTHOR(S): Crescenzi, Orlando; Fraternali, Franca; Picone, Delia; Tancredi, Teodorico; Balboni, Gianfranco; Guerrini, Remo; Lazarus, Lawrence H.; Salvadori, Severo; Temussi, Piero A.
CORPORATE SOURCE: Dipartimento di Chimica, Universita di Napoli Federico II, Naples, I-80134, Italy
SOURCE: Eur. J. Biochem. (1997), 247(1), 66-73
CODEN: EJBCAI; ISSN: 0014-2956
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To discriminate between two general models of antagonism (participation and allosteric), an opioid antagonist lacking the basic nitrogen of tyramine was designed and characterized. Cyclo-[Tyr(Me)2-Tic-], the diketopiperazine of 2,6-dimethyltyrosyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, is a partially rigid opioid antagonist; its pA2 (5.8) is

one smaller than that of N,N-bisallyl-enkephalin but it has a very high binding affinity (10 nM) and has a .delta. selectivity (66 with respect to the binding to .mu. receptors) higher than that of naltrindole. The conformational state of this diketopiperazine, studied under a variety of solvent and temp. conditions by NMR and mol. dynamics, can be described in terms of only three conformers whose relative populations vary widely with solvent. Only one of the three conformers, characterized by a 90.degree. arrangement of the arom. rings of Tyr(Me)2 and Tic similar to those of rigid agonists and of the bioactive conformation of the corresponding linear antagonist, is consistent with the antagonist activity. This finding favors the participation model among the general mechanisms proposed to explain antagonism. Due to the simple compn. of the conformational mixt. and to the rigidity of the mol., it is possible to propose a quant. explanation for the discrepancy between the very high binding affinity (10 nM) and the fairly small in mouse vas deferens value (1.5 .mu.M).

IT **178951-47-8**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(structure of a partially rigid opioid antagonist lacking the basic center)

IT **193897-93-7**
RL: RCT (Reactant)
(structure of a partially rigid opioid antagonist lacking the basic center)

IT **172262-40-7**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(structure of a partially rigid opioid antagonist lacking the basic center design and soln.)

L10 ANSWER 17 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:101287 HCAPLUS
DOCUMENT NUMBER: 126:288045
TITLE: Opioid diketopiperazines. Synthesis and activity of a prototypic class of opioid antagonists
AUTHOR(S): Balboni, Gianfranco; Guerrini, Remo; Salvadori, Severo; Tomatis, Roberto; Bryant, Sharon D.; Bianchi, Clementina; Attila, Martti; Lazarus, Lawrence H.
CORPORATE SOURCE: Biotechnology Center, Univ. Ferrara, Ferrara, I-44100, Italy
SOURCE: Biol. Chem. (1997), 378(1), 19-29
CODEN: BICHF3; ISSN: 1431-6730
PUBLISHER: de Gruyter
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Discovery of high affinity and ultraselective .delta. opioid dipeptide antagonists composed of 2',6'-dimethyl-L-tyrosine (Dmt) and 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) served as the basis for the conformationally restricted diketopiperazine cyclo(Dmt-Tic) and related open chain analogs. These peptides primarily bind to .delta.-opioid receptors: c(Dmt-Tic) displayed 30- to 50-fold higher .delta. affinity (Ki.delta.) than its diastereomeric analogs and more than 4000-fold greater than its Tyr cognate; all of the c(Tyr-Tic) analogs were essentially inactive; c[(N-methyl)Dmt-Tic] lost 5-fold in Ki.delta., while Ki.MU., increased 10-fold to yield a nonselective peptide; and the c(Dmt-Phe) series exhibited considerably reduced binding which indicated a synergism between Dmt and Tic in the binding mechanism. Whereas acetyl-Dmt-Tic linear peptides weakly interacted with opioid receptors,

Ac-Dmt-Tic-NH2, exhibited better .delta. antagonist activity than c(Dmt-Tic) and greater .delta. receptor selectivity (Ki.mu./Ki.delta. = 570). A 3 point attachment hypothesis for the interaction between c(Dmt-Tic) and the .delta. receptor was proposed: hydrophobicity imparted by the arom. rings and the Me groups of Dmt, H bonding through the tyramine OH group, and cation-.pi. interactions were suggested as contributing factors in binding the diketopiperazine in the receptor pocket. Although c(Dmt-Tic) exhibited a weak antagonist activity with mouse vas deferens, this diketopiperazine may provide a scaffolding for the formation of more potent antagonists for potential therapeutic applications.

IT **178951-45-6P 178951-46-7P**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and activity of prototypic diketopiperazine .delta.-opioid antagonists)

IT **178951-47-8P 178951-48-9P**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and activity of prototypic diketopiperazine .delta.-opioid antagonists)

IT **189094-01-7**
RL: RCT (Reactant)
(prepn. and activity of prototypic diketopiperazine .delta.-opioid antagonists)

IT **189093-93-4P 189093-95-6P 189094-05-1P**
189094-07-3P 189094-48-2P 189094-51-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and activity of prototypic diketopiperazine .delta.-opioid antagonists)

L10 ANSWER 18 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:714329 HCAPLUS
DOCUMENT NUMBER: 126:26958
TITLE: Development of potent opioid .delta. antagonists and mixed .mu. agonist/.delta. antagonists
AUTHOR(S): Schiller, P. W.; Schmidt, R.; Wilkes, B. C.; Weltrowska, G.; Nguyen, T. M. -D.; Chung, N. N.; Lemieux, C.
CORPORATE SOURCE: Laboratory Chemical Biology and Peptide Research, Clinical Research Institute Montreal, Montreal, PQ, H2W 1R7, Can.
SOURCE: Pept.: Biol. Chem., Proc. Chin. Pept. Symp., 3rd (1995), Meeting Date 1994, 140-143. Editor(s): Lu, Gui-Shen; Tam, James P.; Du, Yu-Cang. ESCOM: Leiden, Neth.
CODEN: 63QWA5
DOCUMENT TYPE: Conference
LANGUAGE: English

AB An analog of TIPP (Tyr-Tic-Phe-Phe) is reported which is a mixed .mu. agonist/.delta. antagonist with both greatly enhanced .mu. agonist potency and still very high .delta. antagonist activity.

IT **160429-67-4**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(potent opioid .delta. antagonists and mixed .mu. agonist/.delta. antagonists)

L10 ANSWER 19 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:639557 HCAPLUS
DOCUMENT NUMBER: 126:1296
TITLE: Novel opioid peptide analogs with mixed .mu. agonist/.delta. antagonist properties
AUTHOR(S): Schiller, P. W.; Weltrowska, G.; Nguyen, T. M. -D.; Lemieux, C.; Chung, N. N.
CORPORATE SOURCE: Clinical Research Institute Montreal, Montreal, PQ, H2W 1R7, Can.
SOURCE: Pept. 1994, Proc. Eur. Pept. Symp., 23rd (1995), Meeting Date 1994, 632-633. Editor(s): Maia, Hernani L. S. ESCOM: Leiden, Neth.
CODEN: 63MBAO
DOCUMENT TYPE: Conference
LANGUAGE: English
AB In an effort to strengthen the agonist component of TIPP-NH2, the authors substituted 2',6'-dimethyltyrosine (Dmt) for Tyr1. The resulting compd., H-Dmt-Tic-Phe-Phe-NH2 (DIPP-NH2), displayed a potent agonist effect in the GPI assay. This effect was reversed by a low dose of naloxone (Ke = 2.42 nmol dm-3), indicating that it was mediated by receptors. In the MVD assay DIPP-NH2 was a potent antagonist with a value in the subnanomolar range. In comparison with the parent compd. TIPP-NH2, DIPP-NH2 showed 65 times higher receptor affinity and 25 times higher affinity in the opioid receptor binding assays. Redn. of the peptide bond between Tic and Phe in DIPP-NH2 resulted in a pseudopeptide analog, H-Tyr-Tic[CH2-NH]Phe-Phe-NH2, which was an agonist with twice the potency of DIPP-NH2 in the GPI assay and again showed a low Ke value (1.25 nmol dm-3) for naloxone as antagonist.
IT **160429-67-4**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(novel opioid peptide analogs with mixed .mu. agonist/.delta. antagonist properties)

L10 ANSWER 20 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:462678 HCAPLUS
DOCUMENT NUMBER: 125:158369
TITLE: Dmt-TIC-OH, a highly selective and potent .delta.-opioid dipeptide receptor antagonist after systemic administration in the mouse
AUTHOR(S): Capasso, Anna; Guerrini, Remo; Balboni, Gianfranco; Sorrentino, Ludovico; Temussi, Pierandrea; Lazarus, Lawrence H.; Bryant, Sharon D.; Salvadori, Severo
CORPORATE SOURCE: Sch. Pharmacy, Univ. Salerno, Italy
SOURCE: Life Sci. (1996), 59(8), PL 93-PL 98
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Dmt-Tic-OH (DTOH) and Dmt-Tic-Ala-OH (DTAOH), effective antagonists, in vitro, represent new potent opioid dipeptides for the .delta.-opioid receptor (Ki.delta. of 0.022 nM and a selectivity, Ki.mu./Ki.delta., of 150,000 for DTOH; Ki.delta. of 0.285 nM and a selectivity Ki.mu./Ki.delta., of 20,4 for DTAOH). In the present study we considered the pharmacol. activity of these two new .delta. opioid peptide receptor antagonists in vivo. Therefore, we have evaluated their possible antagonistic activity against the antinociception induced by the highly selective .delta. opioid receptor agonist, [D-Ala2]deltorphin II (DEL). Furthermore, these two .delta. opioid peptide receptor antagonists were

injected centrally or peripherally in order to assess their ability to act also after systemic administration. Concurrent i.c.v. injection of DTOH or DTAOH (0.5-1.0-2.0 nM) with DEL (5 nmol) induced a significant redn. of DEL antinociception. By contrast, while DTOH (10-20-40 mg/kg) administered peripherally (i.p., s.c. or i.v.) was also able to reduce DEL antinociception, DTAOH failed. The present results indicate that DTOH is the first opioid dipeptide with .delta. antagonist activity after systemic administration and it could be important in clin. and therapeutic applications.

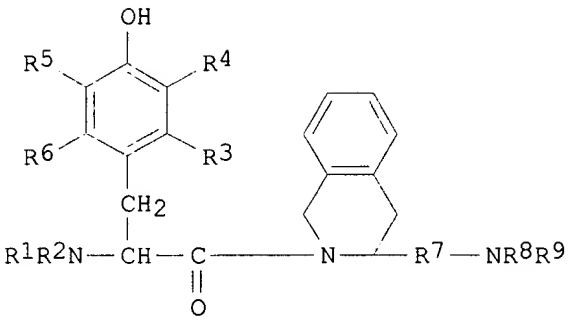
IT **172262-39-4 172262-47-4**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. activity of .delta. opioid receptor antagonists Dmt-Tic-OH and Dmt-Tic-Ala-OH)

L10 ANSWER 21 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:431375 HCAPLUS
DOCUMENT NUMBER: 125:87219
TITLE: Preparation of new peptide derivatives with delta opioid receptor antagonist or mixed mu agonist/delta antagonist effects
INVENTOR(S): Schiller, Peter
PATENT ASSIGNEE(S): Astra Aktiebolag, Swed.
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9606855	A1	19960307	WO 1995-SE918	19950810
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9506561	A	19960229	ZA 1995-6561	19950804
CA 2197566	AA	19960307	CA 1995-2197566	19950810
AU 9534016	A1	19960322	AU 1995-34016	19950810
AU 695175	B2	19980806		
EP 776332	A1	19970604	EP 1995-930752	19950810
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10504837	T2	19980512	JP 1995-508658	19950810
US 5811400	A	19980922	US 1995-532688	19951006
FI 9700823	A	19970227	FI 1997-823	19970227
NO 9700889	A	19970227	NO 1997-889	19970227

PRIORITY APPLN. INFO.: SE 1994-2880 19940830
WO 1995-SE918 19950810

OTHER SOURCE(S): MARPAT 125:87219
GI



I

AB Compds. of formula [I; R1 = H, Me(CH2)n (wherein n = 0-12), CH2CH2Ph, cyclopropylmethyl, allyl, H-Arg; R2 = H, Me(CH2)n (wherein n = 0-12), cyclopropylmethyl, allyl; R3 - R6 = H; or R4 = R5 = H and R3, R6 = C1-6 alkyl; R3 = R5 = R6 = H and R4 = F, Cl, Br, OH, or NO2; R7 = CO, CH2; R8 = H, C1-12 alkyl, aryl-C1-12 alkyl; R9 = linear or branched C1-12 alkyl, aryl-C1-2 alkyl, C1-12 alkyl-linked to a heterocyclic moiety], which show high potency as .delta. antagonists or a mixed .mu. agonist/.delta. antagonist properties with total lack of .mu. antagonist properties, have a low mol. wt. and are highly lipophilic, facilitate passage across the brain blood-barrier, and are useful in therapy, esp. as analgesics and as immunosuppressive agents, are prepd. Thus, Boc-Tic-OH (Tic = 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid residue) was treated with iso-Bu chloroformate in THF at -15.degree. for 3-4 min, coupled with H2N(CH2)3Ph at -15.degree. for 30 min, and stirred with CF3CO2H contg. 3% thioanisole under ice-cooling to give 95% H-Tic-NH(CH2)3Ph.CF3CO2H. The latter compd. was similarly coupled with Boc-Tyr(Boc)-OH in the presence of N-methylmorpholine and deprotected with CF3CO2H to give, after HPLC purifn., 80% H-Tyr-Tic-NH(CH2)3Ph. All compds. showed .delta.-antagonist properties and no .mu. antagonist activity in the guinea pig ileum assay at concns. as high as 10 .mu.M and were either partial or full .mu. agonists in the guinea pig ileum assay. In particular, H-Dmt-Tic-NHCH2CH2Q (Q = CH2Ph, cyclohexyl, 3-indolyl; Dmt = 2',6'-dimethyltyrosine) were potent mixed .mu. agonist/.delta. antagonists.

IT **178752-43-7P 178752-53-9P 178752-57-3P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of new peptide derivs. with .delta. opioid receptor antagonist or mixed .mu. agonist/.delta. antagonist effects as analgesics and immunosuppressants)

L10 ANSWER 22 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:196729 HCAPLUS
DOCUMENT NUMBER: 124:261755
TITLE: Preparation of opioid peptide analogs as .delta. opioid receptor antagonists
INVENTOR(S): Schiller, Peter
PATENT ASSIGNEE(S): Astra Aktiebolag, Swed.
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9535316	A1	19951228	WO 1995-SE721	19950614
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9504311	A	19960122	ZA 1995-4311	19950526
CA 2192484	AA	19951228	CA 1995-2192484	19950614
AU 9528114	A1	19960115	AU 1995-28114	19950614
AU 691630	B2	19980521		
EP 777682	A1	19970611	EP 1995-923629	19950614
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10501807	T2	19980217	JP 1995-502047	19950614
US 5733881	A	19980331	US 1995-507370	19950822
NO 9605457	A	19961218	NO 1996-5457	19961218
FI 9605116	A	19961219	FI 1996-5116	19961219

PRIORITY APPLN. INFO.: SE 1994-2170 19940620
SE 1994-2838 19940825
WO 1995-SE721 19950614

OTHER SOURCE(S): MARPAT 124:261755
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title peptides [I; R1 = H, Me(CH2)n, PhCH2CH2, cyclopropylmethyl, CH2:CHCH2, H-Arg; wherein n = 0-12; R2 = H, Me (CH2)n, cyclopropylmethyl, CH2:CHCH2; wherein n = 0-12; R3 - R6 = H; R4 = R5 = H and R3 = R6 = C1-6 alkyl; R3 = R5 = R6 = H and R4 = F, Cl, Br, OH, NH2, or NO2; R7 = CO, CH2; R8 = H, C1-6 alkyl; R9 = bivalent radical selected from Me(CH2)mCH, Me2CHCH, Me2CHCH2CH, EtCHMeCH, HOCH2CH, MeSCH2CH2CH, Q; wherein p = 0-4; R10 = OH, NH2, Q1, Q2; R11 = H, NO2, F, Cl, Br, iodo; q = 0-3; R12 = CO2H, CONH2, CH2OH, any addnl. amino acid or peptide segment], which are useful in therapy, esp. as analgesics and as immunosuppressive agents, are prepd. Thus, 3.48 g BOP was added to a stirred soln. of 2.8 g Boc-Tic-OH (N-tert-butoxycarbonyl-L-1,2,3,4-tetrahydroquinoline) and 1.33 mL Et3N in CH2Cl2. After 5 min, 1.2 g N-dimethylhydroxylamine hydrochloride and 1.68 mL Et3N were added and the reaction was carried out for 17 h to give, after silica gel chromatog., 65% N-tert-butoxycarbonyl-L-1,2,3,4-tetrahydroquinoline-3-N-methoxy-N-methylcarboxamide, which (1.2 g) was reduced by 190 mg LiAlH4 in Et2O for 1 h to give the aldehyde N-tert-butoxycarbonyl-L-1,2,3,4-tetrahydroquinoline-3-carboxaldehyde (Boc-Tic-H). The resin H-Cha-Phe-O-resin (Cha = cyclohexylalanine) (prepn. given) was washed twice with DMF , successively treated with Boc-Tic-H in DMF contg. 1% AcOH and then portion wise with 115 mg NaBH3CN. After coupling the N-terminal tyrosine and deprotection, the peptide was cleaved from the resin, purified, and lyophilized to give H-Tyr-Tic.PI.[CH2-NH]Cha-Phe-OH.

IT **174860-13-0P 174860-14-1P 174860-15-2P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP

(Preparation); USES (Uses)
(prepn. of opioid peptide analogs as .delta. opioid receptor antagonists, analgesics, and immunosuppressants)

L10 ANSWER 23 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:17570 HCAPLUS
DOCUMENT NUMBER: 124:164281
TITLE: Four different types of opioid peptides with mixed .mu. agonist/.delta. antagonist properties
AUTHOR(S): Schiller, P. W.; Weltrowska, G.; Schmidt, R.; Nguyen, T. M. -D.; Berezowska, I.; Lemieux, C.; Chung, N. N.; Carpenter, K. A.; Wilkes, B. C.
CORPORATE SOURCE: Laboratory Chemical Biology and Peptide Research, Clinical Research Institute Montreal, Montreal, PQ, H2W 1R7, Can.
SOURCE: Analgesia (Elmsford, N. Y.) (1995), 1(4-6), 703-6
CODEN: AALGEB; ISSN: 1071-569X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mixed .mu. agonist/.delta. antagonists are thought to have potential as analgesics with low propensity to produce tolerance and dependence. The first balanced .mu. agonist/.delta. antagonist was the pseudotetrapeptide H-Dmt-Tic.psi.[CH2-NH]Phe-Phe-NH2 (DIPP-NH2[.psi.]; Dmt = 2',6'-dimethyltyrosine; Tic = tetrahydroisoquinoline-3-carboxylic acid), which showed very high .mu. agonist potency in the GPI assay, excellent .delta. antagonist potency in the MVD assay and .mu. and .delta. receptor affinities in the subnanomolar range. The dipeptide deriv. H-Dmt-Tic-NH-(CH2)3-Ph (Ph = phenyl) displayed similarly high .mu. and .delta. receptor affinities and appears to be a mixed partial .mu. agonist/.delta. antagonist. Another class of mixed .mu. agonist/.delta. antagonists are cyclic .beta.-casomorphin analogs contg. a 2-naphthylalanine (2-Nal) residue in the 3-position of the peptide sequence, the prototype being H-Tyr-c[-D-Orn-2-Nal-D-Pro-Gly-]. An analog of this type, H-Dmt-c[-D-Orn-2-Nal-D-Pro-Gly-], also showed balanced .mu. agonist/.delta. antagonist potencies in the subnanomolar range. The novel cyclic opioid peptide H-c(Lys-Dmt-D-Ala-Phe-Asp)-H2 turned out to be yet another prototype of a mixed .mu. agonist/.delta. antagonist.
IT **173927-99-6**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(mixed .mu. agonist/.delta. antagonist opioids as analgesics with low tolerance and dependence)

L10 ANSWER 24 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:7265 HCAPLUS
DOCUMENT NUMBER: 124:75581
TITLE: Conformational analysis of potent and very selective .delta. opioid dipeptide antagonists
AUTHOR(S): Amodeo, P.; Balboni, G.; Crescenzi, O.; Guerrini, R.; Picone, D.; Salvadori, S.; Tancredi, T.; Temussi, P. A.
CORPORATE SOURCE: ICMIB del CNR, via Toiano 6, 80072 Arco Felice, Naples, Italy
SOURCE: FEBS Lett. (1995), 377(3), 363-7
CODEN: FEBLAL; ISSN: 0014-5793
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The .delta. selectivity and antagonism of peptides contg. L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) in second

position can be attributed mainly to the Tyr-Tic unit. These properties can be further enhanced by substituting Tyr1 with 2,6-dimethyl-L-tyrosyl (Dmt). Dmt-Tic-NH2, Dmt-Tic-OH, Dmt-Tic-Ala-NH2 and Dmt-Tic-Ala-OH are all more active and/ or selective than the corresponding [Tyr1]-parent peptides. In fact, the selectivities of Dmt-Tic-OH and Dmt-Tic-Ala-OH are the highest ever recorded for opioid mols. The 1H NMR spectra in a DMSO/water mixt. at 278 K reveal the presence of two similar conformers, characterized by a cis or trans Dmt-Tic bond, in all four peptides. A detailed conformational anal. in soln. of Dmt-Tic-NH2 shows that these conformers have a shape very similar to that of the bioactive conformation of Tyr-Tic-NH2 and to that of naltrindole.

IT **172262-39-4 172262-40-7 172262-47-4**
172262-48-5
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(conformational anal. of potent and selective .delta.-opioid dipeptide antagonists)

L10 ANSWER 25 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:944609 HCAPLUS
DOCUMENT NUMBER: 124:75511
TITLE: .delta. Opioidmimetic antagonists: prototypes for designing a new generation of ultraselective opioid peptides
AUTHOR(S): Salvadori, Severo; Attila, Martti; Balboni, Giofranco; Bianchi, Clementina; Bryant, Sharon D.; Crescenzi, Orlando; Guerrini, Remo; Picone, Delia; Tancredi, Teodorico; et al.
CORPORATE SOURCE: Department of Pharmaceutical Sciences, University of Ferrara, Ferrara, Italy
SOURCE: Mol. Med. (Cambridge, Mass.) (1995), Volume Date 1995, 1(6), 678-89
CODEN: MOMEF3; ISSN: 1076-1551
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tyr-Tic (1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid) and Tyr-Tic-Ala were the first peptides with .delta. opioid antagonist activity lacking Phe, considered essential for opioid activity based on the N-terminal tripeptide sequence (Tyr-D-Xaa-Phe) of amphibian skin opioids. Analogs were then designed to restrain the rotational flexibility of Tyr by the substitution of 2,6-dimethyl-L-tyrosine (Dmt). Tyr and Dmt peptides were synthesized by solid phase and soln. methods using Fmoc technol. or condensing Boc-Dmt-OH or Boc-Tyr(But)-OH with H-L-Tic-OBut or H-D-Tic-OBut, resp. Peptides were purified (>99%) by HPLC and characteristics detd. by 1H-NMR, FAB-MS, m.p., TLC, and amino acid analyses. H-Dmt-Tic-OH had high affinity (Ki.delta. = 0.022 nM) and extraordinary selectivity (Ki.mu./Ki.delta. = 150,000); H-Dmt-Tic-Ala-OH had a Ki.delta. = 0.29 nM and .delta. selectivity = 20,000. Affinity and selectivity increased 8700- and 1000-fold relative to H-Tyr-Tic-OH, resp. H-Dmt-Tic-OH and H-Dmt-Tic-NH2 fitted one-site receptor binding models (.eta. = 0.939-0.987), while H-Dmt-Tic-ol, H-Dmt-Tic-Ala-OH and H-Dmt-Tic-Ala-NH2 best fitted two-site models (.eta. = 0.708-0.801, F 18.9-26.0, $p < 0.0001$). Amidation increased .mu. affinity by 10- to 100-fold and acted synergistically with D-Tic2 to reverse selectivity (.delta. .fwdarw. .mu.). Dmt-Tic di- and tripeptides exhibited .delta. antagonist bioactivity (Ke = 4-66 nM) with mouse vas deferens and lacked agonist .mu. activity (> 10 .mu.M) in guinea-pig ileum prepns. Dmt-Tic analogs weakly interacted with .kappa. receptors in the 1 to >20 .mu.M range. Dmt-Tic opioidmimetic peptides represent a highly potent class of

opioid peptide antagonists with greater potency than the nonopioid .delta. antagonist naltrindole and have potential application as clin. and therapeutic compds.

IT **172262-39-4P 172262-40-7P 172262-41-8P**
172262-42-9P 172262-43-0P 172262-47-4P
172262-48-5P 172339-67-2P 172339-68-3P
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(.delta. opioidmimetic antagonists: prototypes for designing a new generation of ultraselective opioid peptides)

L10 ANSWER 26 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:428717 HCAPLUS
DOCUMENT NUMBER: 122:188168
TITLE: Preparation of peptides as .delta. opioid antagonists.
INVENTOR(S): Schiller, Peter
PATENT ASSIGNEE(S): Aktiebolaget Astra, Swed.
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9415959	A1	19940721	WO 1993-SE1090	19931220
W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2152380	AA	19940721	CA 1993-2152380	19931220
AU 9458448	A1	19940815	AU 1994-58448	19931220
AU 681372	B2	19970828		
EP 678099	A1	19951025	EP 1994-904365	19931220
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
HU 72597	A2	19960528	HU 1995-2041	19931220
JP 08505386	T2	19960611	JP 1993-515914	19931220
US 5602099	A	19970211	US 1994-176938	19940104
ZA 9400055	A	19940705	ZA 1994-55	19940105
CN 1096515	A	19941221	CN 1994-100129	19940105
LV 10962	B	19970420	LV 1995-197	19950629
FI 9503302	A	19950704	FI 1995-3302	19950704
NO 9502650	A	19950830	NO 1995-2650	19950704
PRIORITY APPLN. INFO.:			SE 1993-12	19930105
			WO 1993-SE1090	19931220

OTHER SOURCE(S): MARPAT 122:188168
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. [I; R1 = H, Me(CH2)n, PhCH2CH2, cyclopropylmethyl, allyl, H-Arg; R2 = H, Me(CH2)n, cyclopropylmethyl, allyl, etc.; n = 0-12; R3-R6 =

H, or R4, R5 both = H and R3, R6 both = lower alkyl, or R3, R5, R6all = H and R4 = F, Cl, Br, OH, NH2, NO2; R7 = CO, CH2; R8= H, lower alkyl; R9= Q1-Q7; m = 0-2; R10 = H, F, Cl, Br, iodo; R11 = OH, NH2, Q8, Q9; R12 = H, NO2, F, Cl, Br, iodo; m = 0-2; R13, R14 = CO2H, CONH2, CH2OH, amino acid or peptide segment; with the exceptions of compds. where R1, R2, R3, R4, R5, R6, R8 all = H, R7 = CO, R9 = PhCH2CH, and R11 = Phe-OH, Phe-NH2, OH, NH2], were prepd. Thus, H-Tyr-Tic-Hfe-Phe-OH (Tic = 1,2,3,4-tetrahydroisoquinoline-3-carboxylate; Hfe = homophenylalanyl), was prepd. by solid phase synthesis. I antagonized [Leu5] enkephalin in mouse vas deferens with Ke = 0.169-43.9 nM.

IT **156219-37-3 160429-67-4**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptides as .delta. opioid antagonists)

L10 ANSWER 27 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:259490 HCAPLUS
DOCUMENT NUMBER: 122:71781
TITLE: A highly potent TIPP-NH2 analog with balanced mixed .mu. agonist/.delta. antagonist properties
AUTHOR(S): Schiller, P. W.; Weltrowska, G.; Nguyen, T. M.-D.; Lemieux, C.; Chung, N. N.; Wilkes, B. C.
CORPORATE SOURCE: Lab. Chem. Biol. Peptide Res., Clin. Res. Inst. Montreal, Montreal, PQ, H2W 1R7, Can.
SOURCE: Regul. Pept. (1994), 54(1), 257-8
CODEN: REPPDY; ISSN: 0167-0115
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The tetrapeptide amide H-Tyr-Tic-Phe-Phe-NH2 (TIPP-NH2; Tic = tetrahydroisoquinoline-3-carboxylic acid) has recently been shown to be a moderately potent .mu. opioid agonist and a highly potent .delta. opioid antagonist, thus representing the first known example of a mixed .mu. agonist/.delta. antagonist. In an effort to strengthen the .mu. agonist component of TIPP-NH2, the authors substituted 2',6'-dimethyltyrosine (Dmt) for Tyr1. The analogs H-Dmt-Tic-Phe-Phe-NH2 (DIPP-NH2) and H-Dmt-Tic.PSI.[CH2-NH]Phe-Phe-NH2 (DIPP-NH2[.PSI.]) were both potent .mu. agonists in the GPI assay (IC50 = 13.5 nM and 7.71 nM, resp.) and potent antagonists against .delta. agonists in the MVD assay (Ke .apprx. 0.2 nM and 0.5 nM, resp.). In the rat brain membrane binding assays, DIPP-NH2 and DIPP-NH2[.PSI.] showed very high .mu. receptor affinities (Ki.mu. = 1.19 nM and 0.94 nM, resp.) and .delta. receptor affinities (Ki.delta. = 0.12 nM and 0.45 nM, resp.). DIPP-NH2[.PSI.] represents the first known opioid compd. with balanced mixed .mu. agonist/.delta. antagonist properties.

IT **160429-67-4**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(highly potent tetrapeptide amide analog with balanced mixed .mu. opioid agonist/.delta. opioid antagonist properties)

L10 ANSWER 28 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:450365 HCAPLUS
DOCUMENT NUMBER: 121:50365
TITLE: TIPP analogs: highly selective .delta. opioid antagonists with subnanomolar potency and first known compounds with mixed .mu. agonists/.delta. antagonist properties
AUTHOR(S): Schiller, P. W.; Weltrowska, G.; Nguyen, T. M. D.; Chung, N.; Lemieux, C.; Wilkes, B. C.

CORPORATE SOURCE: Lab. Chem. Biol. Peptides Res., Clin. Res. Inst. Montreal, Montreal, PQ, H2W 1R7, Can.
SOURCE: Regul. Pept. (1994), (Suppl. 1), S63-S64
CODEN: REPPDY; ISSN: 0167-0115
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Analogs of the potent and highly selective .delta.-opioid antagonist H-Tyr-Tic-Phe-Phe-OH (TIPP) (Tic = tetrahydroisoquinoline-3-carboxylic acid) contg. Trp, 3-(2'-naphthyl)alanine (2-Nal), or homophenylalanine (Hfe) in place of Phe3, or p-nitrophenylalanine [Phe(pNO2)] in place of Phe4 exhibited a 1.5-5-fold increase in .delta. antagonist potency against .delta. agonists in the mouse vas deferens (MVD) assay and 3-5-fold enhanced .delta. selectivity. The pseudopeptide H-Tyr-Tic.PSI.[CH2-NH]Phe-Phe-OH (TIPP[.PSI.]) showed excellent stability against enzymic degrdn., high .delta. antagonist potency (Ke .apprx.2.5 nM), no .mu. antagonist properties, and unprecedented .delta. selectivity, being 500 times more selective than the nonpeptide .delta. antagonist naltrindole. The analog H-Dmt-Tic-Phe-Phe-OH (DIPP) (Dmt = 2,6-dimethyltyrosine) displayed a Ke of 0.15 nM and is the most potent .delta. antagonist reported to date. Both H-Tyr-Tic-Phe-Phe-NH2 and DIPP were moderately potent, full .mu. agonists in the guinea pig ileum assay and thus represent the first mixed .mu. agonist/.delta. antagonists known.

IT **156219-37-3**
RL: BIOL (Biological study)
(as .mu. agonist/.delta. antagonist)

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TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

The P indicator for Preparations was not generated for all of the CAS Registry Numbers that were added to the H/Z/CA/CAplus files between 12/27/01 and 1/23/02. Use of the P indicator in online and SDI searches during this period, either directly appended to a CAS Registry Number or by qualifying an L-number with /P, may have yielded incomplete results. As of 1/23/02, the situation has been resolved. Also, note that searches conducted using the PREP role indicator were not affected.

Customers running searches and/or SDIs in the H/Z/CA/CAplus files incorporating CAS Registry Numbers with the P indicator between 12/27/01 and 1/23/02, are encouraged to re-run these strategies. Contact the CAS Help Desk at 1-800-848-6533 in North America or 1-614-447-3698, worldwide, or send an e-mail to help@cas.org for further assistance or to receive a credit for any duplicate searches.

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7	RN	403652-11-9	REGISTRY
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105	RN	195831-72-2	REGISTRY
106	RN	195831-71-1	REGISTRY
107	RN	195831-70-0	REGISTRY

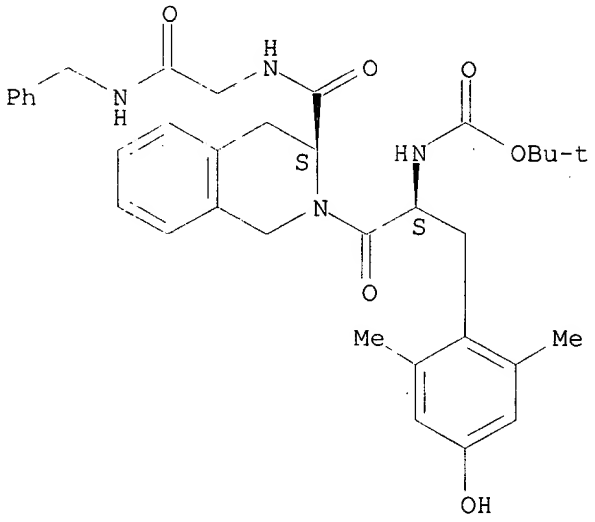
108	RN	195831-69-7	REGISTRY
109	RN	195831-68-6	REGISTRY
110	RN	195831-67-5	REGISTRY
111	RN	195831-66-4	REGISTRY
112	RN	195831-65-3	REGISTRY
113	RN	195831-64-2	REGISTRY
114	RN	195831-63-1	REGISTRY
115	RN	195831-62-0	REGISTRY
116	RN	195831-61-9	REGISTRY
117	RN	195831-60-8	REGISTRY
118	RN	195831-59-5	REGISTRY
119	RN	195831-58-4	REGISTRY
120	RN	195831-57-3	REGISTRY
121	RN	195831-56-2	REGISTRY
122	RN	195831-55-1	REGISTRY
123	RN	195831-54-0	REGISTRY
124	RN	195831-53-9	REGISTRY
125	RN	195831-52-8	REGISTRY
126	RN	194857-88-0	REGISTRY
127	RN	194857-81-3	REGISTRY
128	RN	194857-80-2	REGISTRY
129	RN	194857-79-9	REGISTRY
130	RN	194857-66-4	REGISTRY
131	RN	194857-65-3	REGISTRY
132	RN	194857-64-2	REGISTRY
133	RN	194857-63-1	REGISTRY
134	RN	194857-62-0	REGISTRY
135	RN	194857-61-9	REGISTRY
136	RN	194857-60-8	REGISTRY
137	RN	194857-55-1	REGISTRY
138	RN	194857-54-0	REGISTRY
139	RN	194857-52-8	REGISTRY
140	RN	194857-51-7	REGISTRY
141	RN	193897-93-7	REGISTRY
142	RN	189094-51-7	REGISTRY
143	RN	189094-48-2	REGISTRY
144	RN	189094-07-3	REGISTRY
145	RN	189094-05-1	REGISTRY
146	RN	189094-01-7	REGISTRY
147	RN	189093-95-6	REGISTRY
148	RN	189093-93-4	REGISTRY
149	RN	179091-75-9	REGISTRY
150	RN	179091-74-8	REGISTRY
151	RN	178951-52-5	REGISTRY
152	RN	178951-51-4	REGISTRY
153	RN	178951-48-9	REGISTRY
154	RN	178951-47-8	REGISTRY
155	RN	178951-46-7	REGISTRY
156	RN	178951-45-6	REGISTRY
157	RN	178752-57-3	REGISTRY
158	RN	178752-53-9	REGISTRY
159	RN	178752-43-7	REGISTRY
160	RN	174860-15-2	REGISTRY
161	RN	174860-14-1	REGISTRY
162	RN	174860-13-0	REGISTRY
163	RN	173927-99-6	REGISTRY
164	RN	172339-68-3	REGISTRY
165	RN	172339-67-2	REGISTRY
166	RN	172262-48-5	REGISTRY

167	RN	172262-47-4	REGISTRY
168	RN	172262-43-0	REGISTRY
169	RN	172262-42-9	REGISTRY
170	RN	172262-41-8	REGISTRY
171	RN	172262-40-7	REGISTRY
172	RN	172262-39-4	REGISTRY
173	RN	160429-67-4	REGISTRY
174	RN	156219-37-3	REGISTRY

=> d ide can 19 1 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 174

L9 ANSWER 1 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 403652-25-5 REGISTRY
CN INDEX NAME NOT YET ASSIGNED
FS STEREOSEARCH
MF C35 H42 N4 O6
SR CA
LC STN Files: CAPLUS

Absolute stereochemistry.

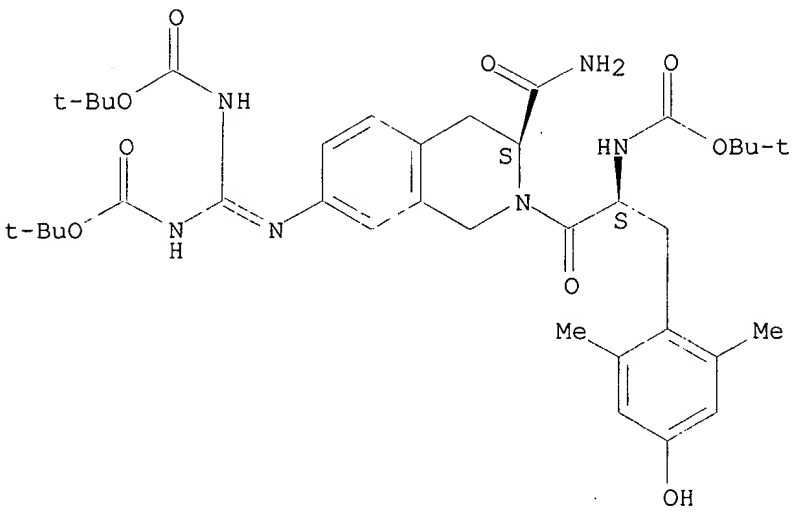


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L9 ANSWER 10 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 349151-66-2 REGISTRY
CN Carbamic acid, [[(3S)-3-(aminocarbonyl)-2-[(2S)-2-[[(1,1-dimethylethoxy)carbonyl]amino]-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-7-isoquinolinyl]carbonimidoyl]bis-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C37 H52 N6 O9
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

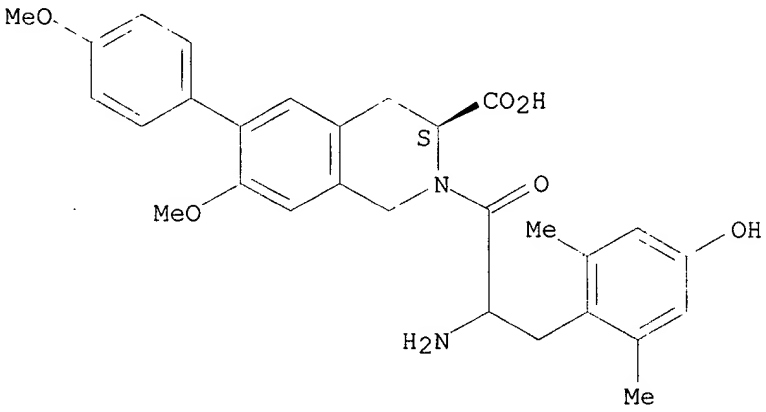


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:92838

L9 ANSWER 20 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 262616-51-3 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-7-methoxy-6-(4-methoxyphenyl)-, (3S)-(9CI). (CA INDEX NAME)
FS STEREOSEARCH
MF C29 H32 N2 O6
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



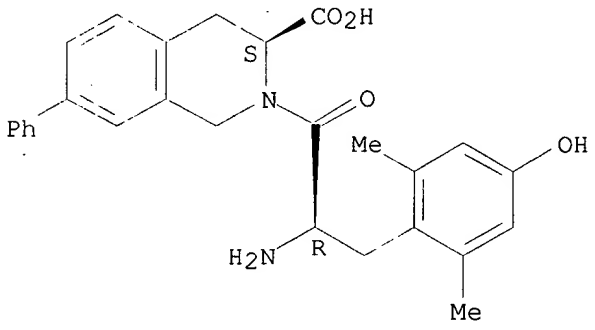
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:245845

L9 ANSWER 30 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 262616-41-1 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2R)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-7-phenyl-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H28 N2 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



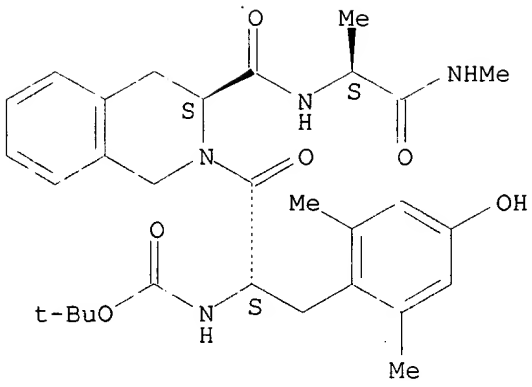
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:245845

L9 ANSWER 40 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 254102-26-6 REGISTRY
CN Carbamic acid, [(1S)-2-[(3S)-3,4-dihydro-3-[[[(1S)-1-methyl-2-(methylamino)-2-oxoethyl]amino]carbonyl]-2(1H)-isoquinolinyl]-1-[(4-hydroxy-2,6-dimethylphenyl)methyl]-2-oxoethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H40 N4 O6
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry. Rotation (+).



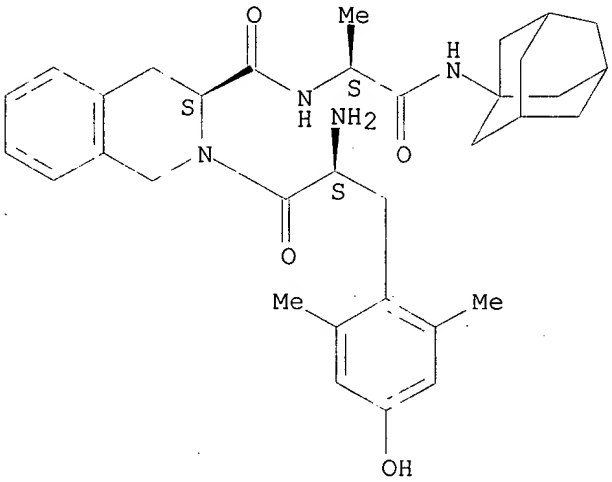
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:73213

L9 ANSWER 50 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 254102-01-7 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-[(1S)-1-methyl-2-oxo-2-(tricyclo[3.3.1.13,7]dec-1-ylamino)ethyl]-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C34 H44 N4 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

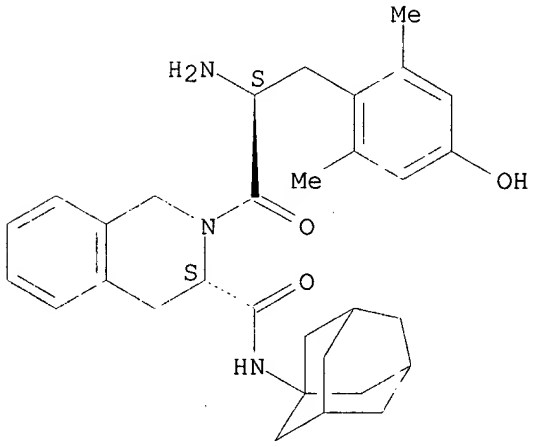
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:235885

REFERENCE 2: 132:73213

L9 ANSWER 60 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 254101-83-2 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-tricyclo[3.3.1.13,7]dec-1-yl-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H39 N3 O3
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry. Rotation (-).



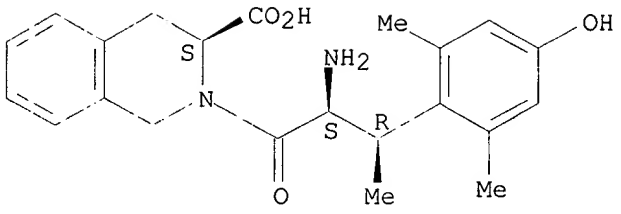
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:235885

L9 ANSWER 70 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 250331-76-1 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2S,3R)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxobutyl]-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H26 N2 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



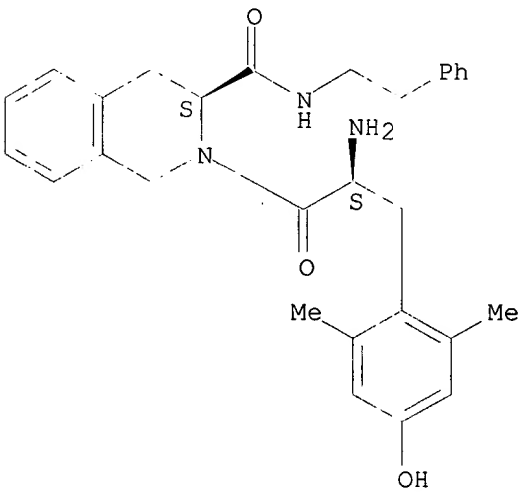
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:347049

L9 ANSWER 80 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 209786-77-6 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[(2S)-2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-(2-phenylethyl)-, (3S)-(9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C29 H33 N3 O3
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

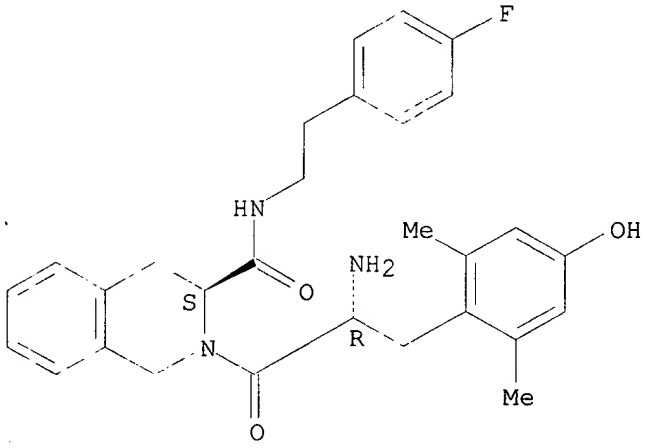
REFERENCE 1: 135:40848

REFERENCE 2: 131:208606

REFERENCE 3: 129:95725

L9 ANSWER 90 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 195831-87-9 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-N-[2-(4-fluorophenyl)ethyl]-1,2,3,4-tetrahydro-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C29 H32 F N3 O3
CI COM
SR CA

Absolute stereochemistry.

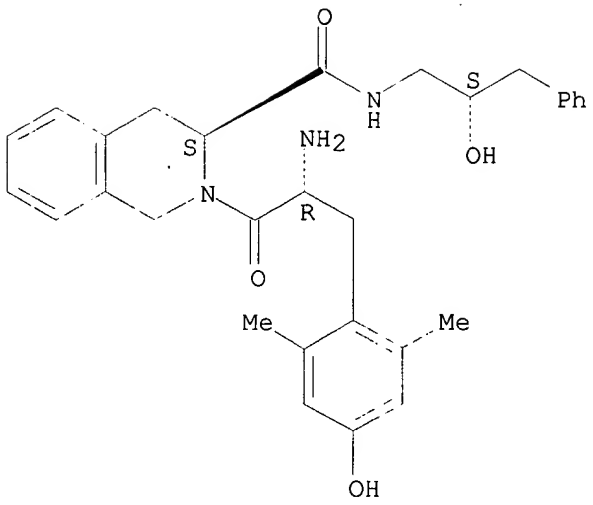


L9 ANSWER 100 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 195831-77-7 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-(2-hydroxy-3-phenylpropyl)-, [3S-[2(S*),3R*(R*)]]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H35 N3 O4 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

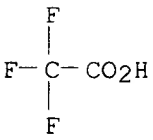
CRN 195831-76-6
CMF C30 H35 N3 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

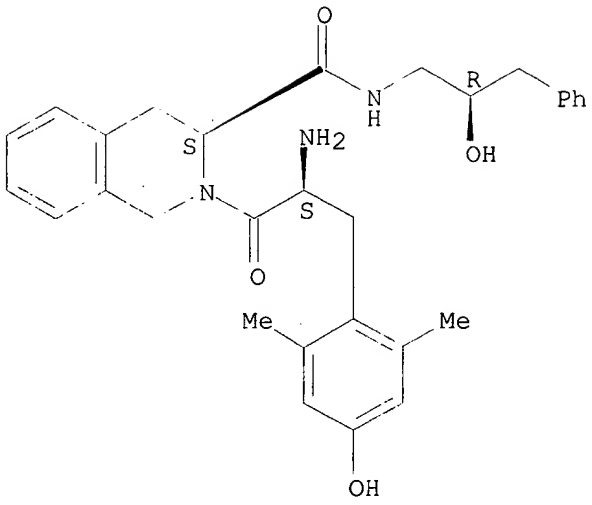
REFERENCE 1: 127:248425

L9 ANSWER 110 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 195831-67-5 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-(2-hydroxy-3-phenylpropyl)-, [3S-[2(R*),3R*(S*)]]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H35 N3 O4 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

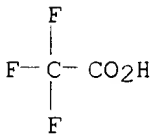
CRN 195831-66-4
CMF C30 H35 N3 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

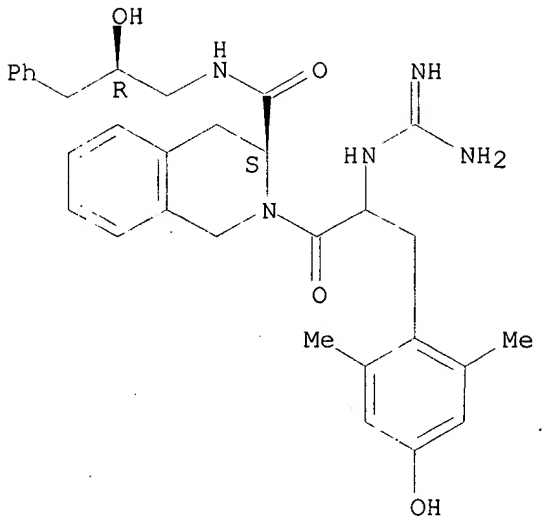
REFERENCE 1: 127:248425

L9 ANSWER 120 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 195831-57-3 REGISTRY
CN 3-Isoquinolinecarboxamide, 2-[2-[(aminoiminomethyl)amino]-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-N-(2-hydroxy-3-phenylpropyl)-, [3S-[3R*(S*)]]-[partial]-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H37 N5 O4 . 2 C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

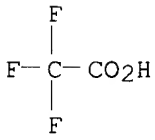
CRN 195831-56-2
CMF C31 H37 N5 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

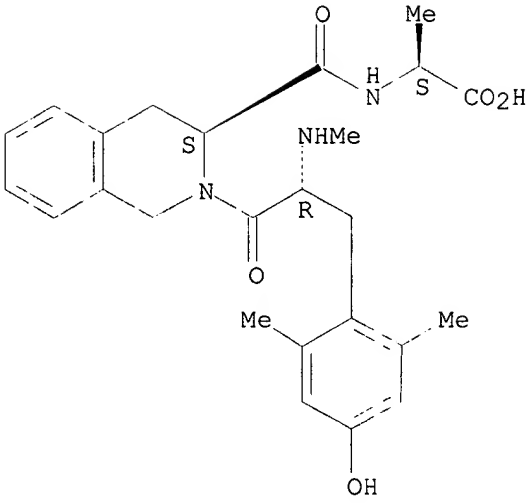
REFERENCE 1: 127:248425

L9 ANSWER 130 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 194857-66-4 REGISTRY
CN L-Alanine, N,2,6-trimethyl-D-tyrosyl-(3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C25 H31 N3 O5 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS

CM 1

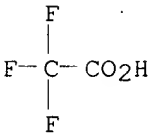
CRN 194857-65-3
CMF C25 H31 N3 O5

Absolute stereochemistry. Rotation (+).



CM 2

CRN 76-05-1
CMF C2 H F3 O2

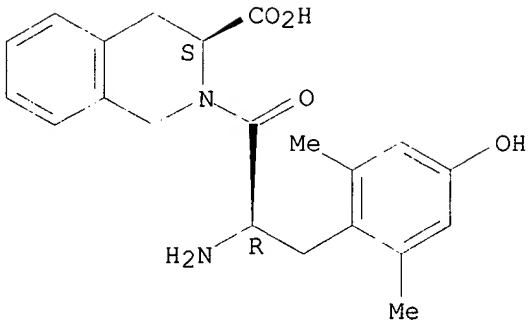


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:214595

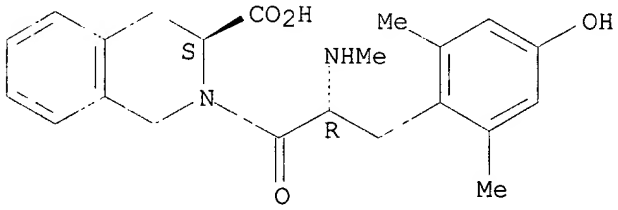
L9 ANSWER 140 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 194857-51-7 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C21 H24 N2 O4
CI COM
SR CA

Absolute stereochemistry. Rotation (+).



L9 ANSWER 150 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 179091-74-8 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 1,2,3,4-tetrahydro-2-[(2R)-3-(4-hydroxy-2,6-dimethylphenyl)-2-(methylamino)-1-oxopropyl]-, (3S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Isoquinolinecarboxylic acid, 1,2,3,4-tetrahydro-2-[3-(4-hydroxy-2,6-dimethylphenyl)-2-(methylamino)-1-oxopropyl]-, [S-(R*,S*)]-
FS STEREOSEARCH
MF C22 H26 N2 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:200061

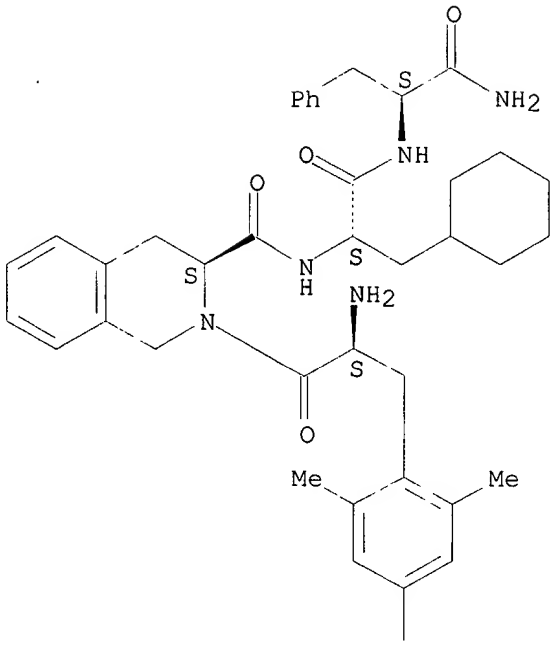
REFERENCE 2: 125:105145

L9 ANSWER 160 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 174860-15-2 REGISTRY
CN L-Phenylalaninamide, 2,6-dimethyl-L-tyrosyl-L-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-3-cyclohexyl-L-alanyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C39 H49 N5 O5
SR CA

LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A

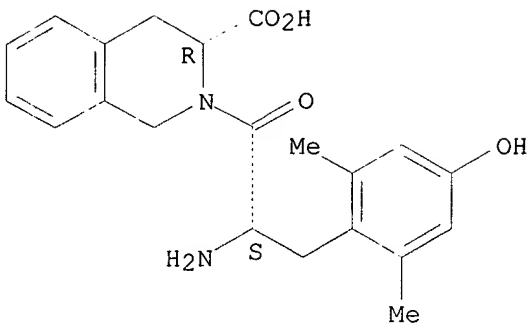
OH

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:261755

L9 ANSWER 170 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 172262-41-8 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[2-amino-3-(4-hydroxy-2,6-dimethylphenyl)-1-oxopropyl]-1,2,3,4-tetrahydro-, [R-(R*,S*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C21 H24 N2 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

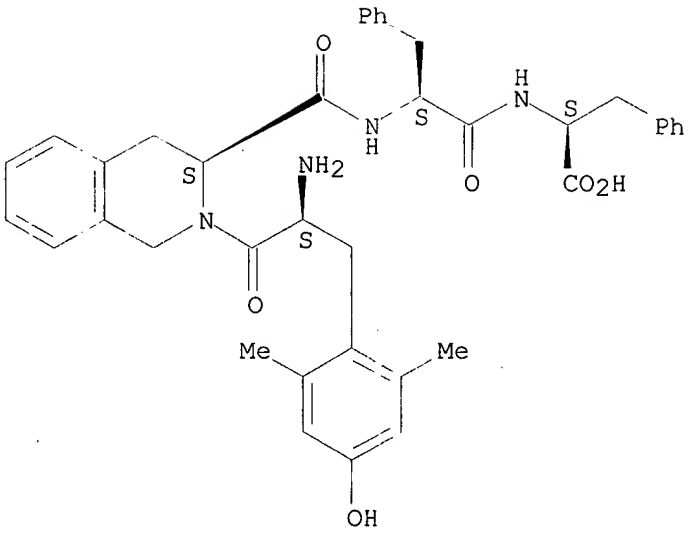
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 125:105145

REFERENCE 2: 124:75511

L9 ANSWER 174 OF 174 REGISTRY COPYRIGHT 2002 ACS
RN 156219-37-3 REGISTRY
CN L-Phenylalanine, 2,6-dimethyl-L-tyrosyl-(3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-L-phenylalanyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Phenylalanine, 2,6-dimethyl-L-tyrosyl-L-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-L-phenylalanyl-
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C39 H42 N4 O6
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:12871

REFERENCE 2: 129:245476

REFERENCE 3: 122:188168

REFERENCE 4: 121:50365